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ESPS PEER-REVIEW REPORT

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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[Y] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] The same title	[Y] High priority for publication
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[ ] Minor revision
[ ] Grade E: Poor		[Y] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

Comments for the Authors The objective of this review is to provide an update on pharmacokinetic drug-drug interactions in the context of liver disease. The authors describe the various factors responsible for the variability in the magnitude of pharmacokinetic drug-drug interactions, the mechanisms responsible for the effect of liver dysfunction on the magnitude of drug-drug interactions due to inhibition or induction of drug-metabolizing enzymes and provide advices for the clinical management of these interactions. This review is a very good work on an interesting topic which has important implications for the clinical management of cirrhotic patients. The following are a few points the authors may wish to consider: Major comments 1) Page 6, in the section 'Mechanisms underlying altered hepatic drug handling in liver disease', for the clear understanding of readers, I recommend to describe more precisely the two categories of drugs according to the hepatic extraction ratio: drugs with high extraction ratio (EH>0.7), i.e. flow-limited drugs for which hepatic clearance is limited by liver blood flow and low extraction ratio (EH<0.3), i.e. capacity-limited drugs for which hepatic clearance is limited by intrinsic metabolic ability of the liver. 2) Page 6, the authors describe the Child and Pugh classification for grading the severity of liver

dysfunction. What about the MELD score? Could it be a more reliable marker of the degree of liver failure and its drug-metabolizing ability? Please incorporate a comment on that question. 3) The role of plasma protein-binding displacement in the erythromycin-quinine interaction needs to be developed for clear understanding of readers, in particular the fact that displacement masks the consequences of enzyme inhibition. Minor issues 4) Some models are now available for quantitative prediction of drug-drug interactions. Are in vivo drug-drug interaction prediction tools available for cirrhotic patients? This might be interesting in order to estimate the magnitude of the interactions. 5) Page 7, 'and the clearances of the two probe drug antipyrine and aminopyrine were found to be proportionally reduced': please precise EH for antipyrine and aminopyrine respectively. 6) It is generally admitted that the plasma protein binding is clinically significant if the bound fraction is above 90%. In this context, it would be interesting to mention the degree of protein binding for theophylline, fluvoxamine, erythromycin, quinine and lidocaine. 7) Spelling/typographical errors: page 16, 'the expression level of this CYP isoform…'