concentrations above or below the previously suggested concentrations thresholds for rifampicin, isoniazid or pyrazinamide.

We think that our study, together with recent studies, not the least from Professor Gumbo and coworkers, calls for standard, routine therapeutic drug monitoring for all TB patients in Denmark; when embarking on a 6 month treatment of a deadly disease, it should be imperative—if the means and methods are available—to monitor whether the doses are correct. However, we still need further evidence on what drug concentrations are necessary, especially in combination treatment, as well as data on the relationships between drug concentrations and adverse effects.

Transparency declarations
None to declare.

References


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Comment on: Pharmacokinetics of the co-administration of boceprevir and St John’s wort to male and female healthy volunteers

Johanna Weiss* and Walter Emil Haefeli

Department of Clinical Pharmacology and Pharmacoepidemiology, University Hospital Heidelberg, Im Neuenheimer Feld 410, 69120 Heidelberg, Germany

*Corresponding author. Tel: +49-6221-56-39402; Fax: +49-6221-56-4642; E-mail: johanna.weiss@med.uni-heidelberg.de

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Sir,

With great interest, we read the recent article in JAC by Jackson et al.1 presenting a study that investigated the drug–drug interaction of boceprevir with St John’s wort (SJW) in healthy volunteers. Given the widespread and often undeclared2 use of this drug, we agree that this combination certainly merits evaluation. When interpreting this data, we do, however, believe that a number of issues should be considered.

The authors repeatedly claim that hypericin is the active component of SJW. However, this is not entirely correct, neither concerning the antidepressant effect of SJW nor concerning its potential to cause pharmacokinetic drug–drug interactions. There is considerable evidence indicating that hypericin is not the only, and is likely not the most important, antidepressant component in SJW (for review see e.g. Butterweck and Schmidt15). Moreover, hypericin has repeatedly been demonstrated not to induce drug-metabolizing enzymes or transporters, indicating that it is not a critical modulator of the drug interaction potential of the individual SJW brand. In contrast, hyperforin is well known to be the major or even the only ingredient responsible for such induction processes mediated by activation of the pregnane X receptor (PXR) that ultimately cause numerous, rather relevant, drug–drug interactions with SJW.4–10

There is a clear correlation between the hyperforin content of SJW preparations, the PXR-activating effect in vitro and the potential for drug–drug interactions in vivo.6–10 For hypericin, evidence for such a correlation is lacking4–8 and in vitro data unequivocally revealed an absence of PXR activation.5,9,10

Hence, hypericin is not a relevant perpetrator in drug–drug interactions and it may be misleading to deduce the interaction potential of a SJW preparation from its hypericin content while ignoring hyperforin. Moreover, because the hyperforin content varies substantially between different SJW preparations and the hyperforin content in the brand used in this study (Ucalm®) is unknown (T. Gaunt, Natures Aid Ltd, Lancashire, UK, personal communication), it would have been more important to quantify hyperforin exposure in the study participants. We are not aware of any other study confirming induction by Ucalm®, and therefore the results of this paper should arrive at the conclusion that this brand does not induce boceprevir metabolism and that it remains open whether this result is also valid for SJW preparations with a considerable propensity for interactions, i.e. those with the highest hyperforin content.

We agree that the influence of SJW on boceprevir pharmacokinetics is expected to be low, because boceprevir is only partly metabolized by CYP3A4.13 Nevertheless, the manufacturer currently advises against the combination of boceprevir with strong CYP3A4 inducers. Apart from this study, data on the effect of enzyme-inducing agents on boceprevir are missing. However, while such data are crucial for the assessment of the interaction potential, this study cannot truly answer this question. Therefore, clinical studies addressing the impact of SJW on drug metabolism should use a compound with a documented inducing potential, and should quantify hyperforin exposure or concurrently use a marker drug (e.g. low-dose midazolam) to confirm that CYP3A4 induction indeed occurred.14

Transparency declarations
None to declare.
References