PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Evaluating the safety and dosing of drugs in patients with liver cirrhosis by literature review and expert opinion: a study protocol
AUTHORS	Weersink, Rianne; Bouma, Margriet; Burger, David; Drenth, Joost; Hunfeld, Nicole; Kranenborg, Minke; Monster-Simons, Margje; van Putten, Sandra; Metselaar, H; Taxis, Katja; Borgsteede, Sander

VERSION 1 - REVIEW

REVIEWER	Benjamin ROLLAND University Hospital of Lille FRANCE
REVIEW RETURNED	26-Jun-2016

GENERAL COMMENTS	Weersink and colleagues submit a protocol article for a systematic assessment of safety and dosing issues with regard to liver cirrhosis. This is actually a very original type of article, and I must confess that I was a bit abashed after my first reading because I was unsure on how to correctly review it. After reflection, I think it is a worthy initiative, and it is more transparent and thorough to submit such a protocol for peer review and to publish it prior to using it. Nonetheless, in my opinion, several issues should be addressed: 1) the described procedure is pretty much similar to that of clinical guidelines (i.e., systematic literature search + expert discussion and final publication of a synthetic consensus document). Therefore, I think the authors' protocol should really benefit from being evaluated using a international instrument for guidelines, such as the APPRAISAL OF GUIDELINES FOR RESEARCH & EVALUATION (AGREE II). Maybe not all the items of the checklist are applicable, but providing an additional table which would check the AGREE II items would strenghten the legitimacy of the protocol. More specifically, this would allow to address some important issues (e.g. conflicts of interest; see below). 2) I do not understand why the literature review should be limited to international peer-reviewed articles. In this instance, addressing international pharmacovigilance databases, such as VigiBase® for example, could also be very useful. Can the authors explain why they did not include this search strategy in their systematic review? 3) In line with the AGREE II statement, the composition of the panel who will issue future drug recommendations is unclear. Will there be some representatives of patient associations, nurses, economists, or GPs, in this expert panel, or merely hepatologists and drug specialists ? How will potential conflicts of interest be managed with the expert group? The authors mention a funding at the end of their

	manuscript. Can they specify if it is a public funder? 4) Please specify if the publication of the recommendations will be only in Dutch or also in English. Please specify in the manuscript whether the future recommendations will be officially 'labeled" by the Dutch Drug Agency?

REVIEWER	Stephan Krähenbühl Clinical Pharmacology & Toxicology University Hospital 4031 Basel Switzerland I have published in the field but have no competing interests
REVIEW RETURNED	12-Jul-2016

GENERAL COMMENTS	The authors describe a systematic approach for dose adjustment in patients with liver cirrhosis. They base their approach on available data in the literature and pretend that it is new, but a closer look into the published studies reveals that this is not the case. I have the following remarks and criticisms: 1. Page 4/line 31: “Portal vein shunting increases oral absorption of some drugs ..”. The authors should be more specific here. Which drugs? 2. Page 4/line 55: The authors state that there are reviews about the subject, but that these reviews are outdated and do not follow a systematic procedure. The authors did unfortunately not do a thorough literature search in this point. Steelandt J et al. suggested a systematic approach based on the Child Pugh Classification (Clin Pharmacokinet 2015;54:1245-58) and Franz CC et al. on the properties of the drugs used (hepatic extraction) (Eur J Clin Pharmacol 2013;69:1565-1573). Franz CC et al. had several previous publications in Drug Safety where they specified their approach. Regarding these publications, the authors should revise their statement about the novelty of their approach. In my view, the approach is not novel, it is just a systematic approach among other systematic approaches to the problem. 3. Page 6/line 27: Primary biliary cholangitis is a not a disease entity; I assume that the authors mean primary biliary cirrhosis (see also page 12/line 15). 4. Page 6/line 29: The authors exclude studies about drug-induced liver injury in patients without cirrhosis. Does this not matter regarding the safety profile of drugs in patients with liver cirrhosis? In other words, are patients with liver cirrhosis more resistant to liver injury than patients without liver cirrhosis? 5. Page 7/line 40: Safety data in patients with liver cirrhosis are difficult to obtain. Studies performed by the pharmaceutical industry are usually short-term pharmacokinetic studies; safety issues have typically to be derived from extrapolation of the pharmacokinetic data and from case reports. 6. Page 8/line 18: Only few drugs are eliminated exclusively by the liver. Renal impairment is therefore also a consideration in these patients regarding drug safety. Patients with liver cirrhosis typically can have low serum creatinine levels despite impaired glomerular filtration. How do the authors approach this problem? 7. Page 10/line 18: The panel may be too large. The larger the panel, the more difficult it will be to reach consensus. 8. Page 12/Table 3: Osmotic laxatives is too broad in relation to

	hepatic encephalopathy. Lactitol and lactulose are typically used; the mode of action is not related to the laxative effect of these drugs. 9. Page 12/line 39: “To our knowledge …”. Similar issue as discussed in point 2. Look at the studies mentioned in point 2 and then decide whether this sentence should be corrected.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Benjamin ROLLAND
Institution and Country: University Hospital of Lille, FRANCE
Competing Interests: None

Weersink and colleagues submit a protocol article for a systematic assessment of safety and dosing issues with regard to liver cirrhosis. This is actually a very original type of article, and I must confess that I was a bit abashed after my first reading because I was unsure on how to correctly review it. After reflection, I think it is a worthy initiative, and it is more transparent and thorough to submit such a protocol for peer review and to publish it prior to using it.

We thank the reviewer for his careful evaluation of our study protocol. Our intention for submitting this protocol was indeed to be transparent in the method we used to achieve our advices. Also, peer review from external experts can strengthen our method.

Nonetheless, in my opinion, several issues should be addressed:
1) the described procedure is pretty much similar to that of clinical guidelines (i.e., systematic literature search + expert discussion and final publication of a synthetic consensus document). Therefore, I think the authors' protocol should really benefit from being evaluated using a international instrument for guidelines, such as the APPRAISAL OF GUIDELINES FOR RESEARCH & EVALUATION (AGREE II). Maybe not all the items of the checklist are applicable, but providing an additional table which would check the AGREE II items would strenghten the legitimacy of the protocol. More specifically, this would allow to address some important issues (e.g. conflicts of interest; see below).

We share the opinion of the reviewer that this is no standard study protocol.
The literature review part is only one of the six steps we follow, so the PRISMA-checklist is in our opinion not the best fit. We thank the reviewer for his suggestion of the AGREE II instrument. The AGREE II instrument seems to fit our study. We provided a supplementary file with a checklist for the AGREE II instrument. In evaluating our method with the AGREE II instrument we came across a few issues we did not clarify well enough in the manuscript (see also editorial comment no 2). In the supplementary file we describe where we added extra information. In the discussion (page 13) we refer to the AGREE II instrument.

2) I do not understand why the literature review should be limited to international peer-reviewed articles. In this instance, addressing international pharmacovigilance databases, such as VigiBase® for example, could also be very useful. Can the authors explain why they did not include this search strategy in their systematic review?

We agree with the reviewer that pharmacovigilance databases may be a very useful tool for evaluating the safety of a drug. The proposed strategy is an interesting possibility that – as far as we know - has not been used for drugs in liver cirrhosis, and needs to be explored and validated. Therefore, it falls beyond the scope of the current project. Data from pharmacovigilance databases are used to signal potential side effects of drugs in a general population. The quality of reports varies:

for many patients underlying diseases (and comorbidities) are insufficiently documented. Also, pharmacokinetic data are seldom present. Hence, a separate study is needed to answer the question how these databases might answer questions about safety and dosing of drugs in liver cirrhosis.

3) In line with the AGREE II statement, the composition of the panel who will issue future drug recommendations is unclear. Will there be some representatives of patient associations, nurses, economists, or GPs, in this expert panel, or merely hepatologists and drug specialists ? How will potential conflicts of interest be managed with the expert group? The authors mention a funding at the end of their manuscript. Can they specify if it is a public funder?

On page 10 and 11 of our manuscript we describe the members of the expert panel and their role in the panel. We decided to include (1) health care professionals with expertise regarding our two main outcomes; altered safety or pharmacokinetics in patients with liver cirrhosis, (2) representatives of the specialists responsible for prescribing (hepatologist, general practitioner) and dispensing (clinical and community pharmacist), and (3) specialists responsible for the clinical decision support systems. Also, one of the members is a methodological expert (epidemiologist). For this project, we work in close collaboration with the Dutch Liver patients' association. Together we decided that there will be no representative in the expert panel since the discussions are too difficult and professional. In our overarching project group there is a representative included. In the manuscript we changed the sentences about the expert panel, to make the composition clearer. On page 11 we added extra information regarding the conflicts of interest of the expert panel and how they will be managed. As also requested by AGREE II point 23.
With regard to the study funding, we expanded our text at the end of our manuscript. In our funding statement we added that our (public) funder had no influence on the content of the study protocol (see page 16), in accordance with AGREE II point 22.

4) Please specify if the publication of the recommendations will be only in Dutch or also in English. Please specify in the manuscript whether the future recommendations will be officially 'labeled'' by the Dutch Drug Agency?

The summary of findings tables in the assessment report will be in English. However, since the advices will be implemented in Dutch clinical decision support systems, the specific advices will be in Dutch. We have added this in the manuscript (page 11).
For the time being, the recommendations will not be officially 'labeled' by the Dutch Medicines Evaluation Board (MEB). This is mainly because of the juridical character of official drug labels, and the procedures accompanying changes in the SmPC's. However, we are exploring possibilities to improve the drug label with one the members of the expert panel who is assessor of the Dutch Medicines Evaluation Board. We added this comment as a research question for further research in the manuscript (see page 14).

Reviewer: 2
Reviewer Name: Stephan Krähenbühl
Institution and Country: Clinical Pharmacology & Toxicology University Hospital, 4031 Basel, Switzerland
Competing Interests: I have published in the field but have no competing interests

The authors describe a systematic approach for dose adjustment in patients with liver cirrhosis. They base their approach on available data in the literature and pretend that it is new, but a closer look into the published studies reveals that this is not the case.

We would like to thank the reviewer for his valuable feedback.

As we explain in point 2, the generation of dosing advices for drugs in these patients is indeed not new, but in our opinion our total approach is new.

I have the following remarks and criticisms:
1. Page 4/line 31: “Portal vein shunting increases oral absorption of some drugs ..”. The authors should be more specific here. Which drugs?

According to the well-stirred model, drugs with a high hepatic extraction ratio are vulnerable for changes in liver blood flow (e.g. portal vein shunting). We have changed the sentence.

2. Page 4/line 55: The authors state that there are reviews about the subject, but that these reviews are outdated and do not follow a systematic procedure. The authors did unfortunately not do a thorough literature search in this point. Steelandt J et al. suggested a systematic approach based on the Child Pugh Classification (Clin Pharmacokinet 2015;54:1245-58) and Franz CC et al. on the properties of the drugs used (hepatic extraction) (Eur J Clin Pharmacol 2013;69:1565-1573). Franz CC et al. had several previous publications in Drug Safety where they specified their approach. Regarding these publications, the authors should revise their statement about the novelty of their approach. In my view, the approach is not novel, it is just a systematic approach among other systematic approaches to the problem.

We are aware of these articles and agree that our study is not the first systematic approach to this problem.
There are several studies predicting the changes in pharmacokinetics of drugs in liver cirrhosis and most give dosing recommendations. [Franz CC et al. Eur J Clin Pharmacol 2013;69:1565-1573; Delco F et al. Drug Saf 2005;28(6): 529-545;Tchambaz L et al. Drug saf 2006;29 (6):509-522; Schlatter C et al. Drug saf 2009;32(7): 561-578; Steelandt J et al. Clin Pharmacokinet 2015;54:1245-58; Johnson TN et al. Clin pharmacokin 2010;49 (3):189-206.; Edginton AN, et al. Clin pharmacokin 2008;47(11):743-752.] These studies follow a systematic approach, mainly based on the well-stirred model. The generation of dosing recommendation is also one of the aims of our study. All the studies above are of great value and can be very useful for healthcare professionals. However, they can be difficult to obtain for a busy health care professional not frequently working with patients with liver cirrhosis. So, what we think is new regarding our study, is the generation of a safety classification in combination with dosing advices and the implementation of these advices in clinical decision support systems.
We included the suggested references and revised this paragraph (see page 4).

3. Page 6/line 27: Primary biliary cholangitis is a not a disease entity; I assume that the authors mean primary biliary cirrhosis (see also page 12/line 15).

We intentionally used ‘cholangitis’ instead of ‘cirrhosis’. The terminology of primary biliary cirrhosis has recently been changed into primary biliary cholangitis. Beuers U, et al. Changing nomenclature for PBC: From 'cirrhosis' to 'cholangitis'. Hepatology. 2015;62(5):1620.

4. Page 6/line 29: The authors exclude studies about drug-induced liver injury in patients without cirrhosis. Does this not matter regarding the safety profile of drugs in patients with liver cirrhosis? In other words, are patients with liver cirrhosis more resistant to liver injury than patients without liver cirrhosis?

Studies showing a higher risk of hepatotoxicity in patients with cirrhosis will be included as they meet our PICO (study in patients with liver cirrhosis). We do not include studies with drug-induced liver injury in patients without cirrhosis, as in general, patients with liver cirrhosis are not at increased risk for developing drug-induced liver injury [Lee WM. Drug-induced hepatotoxicity. NEJM 2003; 349

(5):474-485]. However, in clinical practice there are issues regarding the safety profile of drugs that matter. Such issues are discussed in the expert panel, and expert-based experiences will be included in the assessment report. To make this clear, we added the following sentence to the manuscript (page 10):Comments and opinions of the panel will be added to the initial report, such as recommendations for therapeutic drug monitoring or extra monitoring of liver function tests.

5. Page 7/line 40: Safety data in patients with liver cirrhosis are difficult to obtain. Studies performed by the pharmaceutical industry are usually short-term pharmacokinetic studies; safety issues have typically to be derived from extrapolation of the pharmacokinetic data and from case reports.

We agree with the reviewer that there is probably not much data about the safety of drugs in cirrhotic patients. We do, however, think it is important to include the available data about safety. We think we will miss information if we only consider pharmacokinetic data.
Even so, in case of few data we hope the combination of literature and expert opinion allows us to give specific advices.

6. Page 8/line 18: Only few drugs are eliminated exclusively by the liver. Renal impairment is therefore also a consideration in these patients regarding drug safety. Patients with liver cirrhosis typically can have low serum creatinine levels despite impaired glomerular filtration. How do the authors approach this problem?

Impaired renal function as complication of liver cirrhosis is indeed a problem we are not discussing in our manuscript. Drugs mainly excreted by the kidneys can accumulate due to hepatorenal syndrome which can be dangerous for drugs with a narrow therapeutic range. Because clinical studies mostly include stable cirrhotic patients, there will be little or no data about the effects of hepatorenal syndrome on drug pharmacokinetics. In our opinion, it is important for prescribers to be aware of this problem. For drugs with mainly renal clearance and a narrow therapeutic range, we will discuss the issue with the expert panel and if it is deemed necessary, specifically mention it in the assessment report. Also, information on the hepatorenal syndrome will be added to our website.

7. Page 10/line 18: The panel may be too large. The larger the panel, the more difficult it will be to reach consensus.

The size of the panel is based on experiences of Health Base Foundation and The Royal Dutch Pharmacists Association. In other expert panels we experience that it is most important that all involved experts are represented in the panel. For this reason, we proposed the current composition of the expert panel. In our protocol we anticipate on a potential situation where it will be more difficult to reach consensus: (see page 10: ‘If there are different interpretations within the expert panel, these will be included as ‘expert comments’ in the assessment report.’

8. Page 12/Table 3: Osmotic laxatives is too broad in relation to hepatic encephalopathy. Lactitol and lactulose are typically used; the mode of action is not related to the laxative effect of these drugs.

Thank you for this comment. We have changed ‘osmotic laxatives’ into lactitol and lactulose.

9. Page 12/line 39: “To our knowledge …”. Similar issue as discussed in point 2. Look at the studies mentioned in point 2 and then decide whether this sentence should be corrected.

We agree with the issue mentioned by the reviewer in point 2. In this paragraph we are, however, discussing another issue. We have deleted the particular sentence because it was indistinct and vague.

VERSION 2 – REVIEW

REVIEWER	Benjamin ROLLAND CHU Lille, Univ Lille, Lille, France Competing interests with the following industrial firms: ETHYPHARM, INDIVIOR, BOUCHARA-RECORDATI, LUNDBECK, ASTRA-ZENECA, GILEAD, BRISTOL-MYERS-SQUIBB, OTSUKA, and SERVIER
REVIEW RETURNED	25-Aug-2016

GENERAL COMMENTS	I thank the authors for their responses and have no further request. I will be looking forward to reading their reports on drug safety for liver disease.