Author's response to reviews

Title: Peroxisome Proliferators-Activated Alpha Agonist Treatment Improves Hepatic Damage in Rats with Obstructive Jaundice: An Experimental Study

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Author's response to reviews: see over
COVER LETTER FOR REVISIONS

Dear Editor,

First of all, thanks to all reviewers very much for their criticisms. All the questions are answered one by one and the suitable changes are performed in the article as you suggested. You can make the necessary adjustments.

Title: Peroxisome Proliferators-Activated Alpha Agonist Treatment Improves Hepatic Damage in Rats with Obstructive Jaundice: An Experimental Study

C: criticism
A: author’s reply

R: revision provided

In this manuscript, Cindoruk and colleagues report that a fenofibrate treatment for 6 days reduces the cholestatic effects of bile duct ligation in rats. They suggest that short-term administration of fenofibrate to bile-duct ligated rats exerts beneficial effects on hepatocellular apoptosis. This is an interesting study reporting significantly novel observations. However, a number of important questions (listed below) may be addressed prior publication.

C: The clinical relevance of this study is unclear. How the observations reported here may be extrapolated to the human situation? Indeed, fibrates, as peroxisome proliferators, have significantly different effects in rodents and humans. Are there any situations in which human patients may profit of such a short-term treatment with fibrates?
A: There are important clues about the increasing long term effect of PPAR agonists over tumor growth. However, short term administration of fenofibrates can be used especially in patients who are being planned to be undertaken to an operation in a short time. Although it was seen that fibrates have different effects, there has been no direct relation with time. Only one study is not enough for to say it’s suitable for clinical practice, but our study will be an example for the future experimental studies.

C: In accordance with the present study, the beneficial effects of fenofibrate for cholestatic patients with asymptomatic PBC as already been reported (Ohira H et al. Am J Gastroenterol 2002). However, the observation that fenofibrate reduces apoptosis and increases bile duct number in livers of BLD animals is truly original. Nevertheless, the authors do not discuss neither the significance nor the mechanism of the increased number of bile ducts. This is an important issue since this observation is the most original result from this study.
A: I agree with your criticism. Increasing effect of fenofibrates on bile ducts can effect the compensatory mechanism in cholestatic period.

R: This subject is added to the discussion. Page 9 paragraph 2

C: While the fenofibrate treatment significantly reduces the serological parameters analysed, most remains drastically high when compared to the Sham control animals. This means that fenofibrate only partially corrects the effects of bile-duct ligation. Do the authors believe that longer exposure to the drugs may further improve the response and restore the liver functions? This should be discussed.
A: You're right. High levels of liver function test in treatment group than sham group can be explained by the short treatment period.

R: This is added to the discussion as 3rd paragraph. Page 9, 3rd paragraph

C: The authors state that “decreasing the synthesis of bile acids, and thus affecting the bilirubin levels indirectly” (page 8). There is no reference to support this statement and to the best of our knowledge there are no evidence that the level of bilirubin is directly or indirectly related to bile acid synthesis. Could the authors indicate what the evidences of such a statement are?

R: Revision provided.

C. Fibrates are known to induce bilirubin conjugation with a glucuronide group, the major eliminating pathway for this pigment. Therefore, the authors should discriminate whether the reduction of total bilirubin in fenofibrate-treated animals reflects a reduction of the conjugated or non-conjugated bilirubin.
A: This part was corrected in the previous criticism.

C: The authors indicate that “BLD is associated with intrahepatic bile acid overload”. Did they measure the bile acid content in the liver of BLD and BLD-treated animals? This is required to assess the importance of bile acid reduction as a mediator of the beneficial effects of fenofibrate in their study.
A: Total bile acid in serum has measured.

R: Revision provided

C: A large number of approximations and inconsistencies are found all along the manuscript. This manuscript should be extensively edited, or at least carefully read and corrected by the authors themselves.
A: The text was re-explored and the corrections were done.
Below are some examples of the most important discrepancies:

C: The authors mix the terms apoptosis/necrosis. However, these are 2 different biological processes. They should use the appropriate term in their sentences.

A: You’re right. Corrections were done.

R: Revision provided.

C: In the last sentence of the introduction, they indicate that they aim at measuring also the effects of fenofibrate on oxidative stress. However, no data are presented for this parameter.

A: You’re right. We have seen that there had been a writing error.

R: The measurement method of MDA was added to the material and method. The related changes were done in the results and discussion.

C: As presented in the discussion the true effects of fibrates on NFkB activity is very confusing. In the 3rd paragraph the authors indicate that “PPARalpha agonists activate NFkB”, while in the 4th one they mention that “anti-inflammatory effects of fibrates on human CRP expression in hepatocytes is based on up-regulation of IκBα resulting in reduced NFkB activity.” This should be clarified.

A: You’re right. We have changed the 4th paragraph because of making confusion.

R: “It has been shown that anti-inflammatory action of fibrates on human C-reactive protein expression in hepatocytes is based on up-regulation of cytosolic inhibitor of NF-κB, IκBα resulting in reduced NF-κB activity” This sentences was taken of from the text.

C: All along the discussion the author mention that the beneficial effects of fenofibrate are PPARalpha-mediated. However, they cannot exclude the possibility that fenofibrate exert PPARalpha-independent effects. To state that PPARalpha is truly responsible for the change observed the authors need to compare with similar treatments in KO animals. It would be more appropriate to discuss the effect of fenofibrate rather than those of the receptor.

A: The basic effect of fenofibrate is the PPAR activation. For this reason, this way of statements was used in the text. If the study had been done in KO animals, it would have been better. However, it was seen similar in the several studies about fenofibrates in the literature so that we mentioned about the effects of PPAR.
C: What is tissue MDA level in table 1? How was it determined?
A: The way of MDA measurement added to material and Method. The relation between MDA results and oxidative injury was added to the text.

C: In fig. 2 authors indicate a p value lower than 0.05, while in the corresponding result section, they mention a p<0.001.

R: Revision provided

C: Numerous grammatical and orthography errors have to be corrected.

R: Revision provided.