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
1) As you have mentioned in your previous suggestions, we tried to use Kruskal-Wallis test however, I think we were not successful to present our results in a clear way. We are very sorry for this inconvenience.

We have first applied Kruskal-Wallis test to find if any significant difference exists between groups. If there is a significant difference between groups, then we have done paired comparisons by using Mann-Whitney U test.

Since we have 4 groups, we have divided the conventional p value (0.05) by 4, the resultant number is 0.0125. This value is considered as the significant p value for paired comparisons (<0.01).

2) We have used Kruskal-Wallis test first and then we have done paired comparisons (Mann Whitney U)

3) In our previous manuscript, the tables are not self-explanatory and we are sorry for this. Actually, we have done paired comparisons for groups which have significant p value in Kruskal-Wallis test but we did not explain this in the manuscript. As you will see, we have added information about statistical methodology in the “materials and methods” section and in the tables as a footnote (yellow-highlighted).

4) In order to reply the fourth part of the comments, I have pasted the suggestions below and added the relevant explanation.

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. Below are some examples of the most important discrepancies:
a. The authors mix the terms apoptosis/necrosis. However, these are 2 different biological processes. They should use the appropriate term in their sentences. 

**ANSWER:** You are absolutely correct. We have exchanged the term “necrosis” to “apoptosis”.

b. 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.

**ANSWER:** Malonilialdehyde (MDA), which is the last product of oxidative stress, is measured in liver tissue (Table 1, last row)

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 hepacytes is based on up-regulation of IkBa resulting in reduced NFkB activity.” This should be clarified.

**ANSWER:** We have deleted the “anti-inflammatory effects of fibrates on human CRP expression in hepacytes is based on up-regulation of IkBa resulting in reduced NFkB activity.” part in the discussion. Instead, the anti-inflammatory effect of fenofibrate is explained by PPARalpha stimulation, and subsequent silencing of genes involved in the inflammatory response (page 10).

d. 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.
ANSWER: We are totally in agreement with you. We tried to exchange the statements such as “The effect of PPARalpha induction” to “The effect of fenofibrate treatment”.

e. What is tissue MDA level in table 1? How was it determined?

ANSWER: In table 1, in the last row tissue MDA levels are shown and expressed as (nmol/mg protein). The methodology of MDA assay is in the fifth page of the manuscript (a copy is below).

**Determination of Tissue MDA (page 5, Materials and Methods)**

Tissue MDA assays were performed according to Ohkawa et al. [16]. Briefly, MDA, the product of lipid peroxidation, reacts with thiobarbituric acid under acidic conditions at 95°C to form a pink-colored complex with an absorbance at 532 nm. 1,1,3,3-Tetraethoxypropane was used as the standard. The results are expressed as nmol/mg protein.

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

ANSWER: We have revised the statistical calculations all through the manuscript and as you may see in the revised version, p value in figure 2 and in the corresponding results section is <0.01.

All revisions in the manuscript is yellow-highlighted. We hope that we had fulfilled the requested revisions and we are looking forward to hear from you.

Sincerely.