Author’s response to reviews

Title: The incidence, risk factors, and clinical outcomes of rhabdomyolysis associated with fenoverine prescription: a retrospective study in South Korea (1999–2014)

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Version: 1 Date: 21 Feb 2020

Author’s response to reviews:

We appreciate your positive comments for our manuscript. Below are our responses to “Reviewer’s comments.

GENERAL COMMENTS:
The issue that I have with the manuscript is of methodological nature. While I appreciate the effort that has been done in order to unearth many cases of fenoverine toxicity the authors go on to make many subgroups based on dichotomous comparisons. While that is attractive (liver cirrhosis vs not, acute renal failure vs. not, mortality vs survival) this opens the door for spurious results just because of the multiple comparisons. My point is that the subgrouping is not beneficial to get the message across.

We partially agree that our diverse comparisons are confusing. As nephrologists, we made various comparisons to reveal the relationship between acute renal failure, chronic liver disease, and mortality.

I had asked "I would like to see where fenoverine is being marketed and which countries still have registered the drug". The rebuttal does not contain an answer while I think that this is vital.

By searching the internet, fenoverine is being marketed and registered in several countries including South Korea, Singapore, India, Mexico, Georgia, and Colombia.
I see that a multivariable analysis is difficult to do. However, somebody who had died in January 1999 may have received other type of care than a patient dying in 2014. Probably the prognosis of rhabdomyolysis has improved during the study period due to better (ICU) care. So retrospective studies have their disadvantages and this should be acknowledged.

We appreciate your critical comments. We added limitations on the section of “Discussion”. Please check it (line 17-20, page 9).

The authors have added several limitations in their manuscript and I am fine with that.

I am not sure why you use the term severe hepatic derangement instead of Child-Pugh "C" classification. The Child Pugh classification is recognized and well known in the community. Please use Child Pugh classification throughout.

-The description of ‘severe hepatic derangement’ was used in only “Table” for the simplicity and understanding. We also described this on the section of Methods (line 27-29, page 4).

The authors use the term "chronic hepatopathy" in the discussion related to reference 19. I am not sure what that is, or what that refers to. Please correct. (Upon reading the paper states "une hepatopathie chronique (alcoolique, post-virale, hemochromatose) : 16 cas.; probably referring to chronic liver disease).

-We appreciate your comment. We changed “chronic hepatopathy” into “chronic liver disease” (line 32, page 7).

I am grateful to the authors that they have provided a reference to the definition of rhabdomyolysis

REQUESTED REVISIONS:
The issue that I have with the manuscript is of methodological nature. While I appreciate the effort that has been done in order to unearth many cases of fenoverine toxicity the authors go on to make many subgroups based on dichotomous comparisons. While that is attractive (liver cirrhosis vs not, acute renal failure vs not, mortality vs survival). This opens the door for spurious results just because of the multiple comparisons. My point is that the subgrouping is not beneficial to get the message across.

-We partially agree your proposal that the subgrouping is not beneficial to get the message across. However, we think that subgrouping sometimes helps us to understand the results in more detail and intensively. As nephrologists, we focused on comparisons to reveal the relationship between acute renal failure, chronic liver disease, and mortality in our manuscript. We don’t think that our dichotomous comparisons resulted in spurious results.

ADDITIONAL REQUESTS/SUGGESTIONS:
Please report the data as is, just one series of patients without trying to group them. This introduces a major source of bias. You might want to mention that the majority of patients suffered from chronic liver disease, but the association / correlation is not causation, despite that it is highly likely. If you report that 19/22 patients with fenoverine who developed rhabdomyolysis had liver disease a ~correlation~ will be clear.
-We appreciate your considerate comment. We modified our description as you suggest. Please check it (line 17-18, page 5, line 21~24, page 5).