Reviewer’s report

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

Version: 0 Date: 05 Feb 2020

Reviewer: Research Square Reviewer 1

Reviewer's report:

PEER REVIEWER ASSESSMENTS:

OBJECTIVE - Full research articles: is there a clear objective that addresses a testable research question(s) (brief or other article types: is there a clear objective)?
Yes - there is a clear objective

DESIGN - Is the current approach (including controls and analysis protocols) appropriate for the objective?
No - there are minor issues

EXECUTION - Are the experiments and analyses performed with technical rigor to allow confidence in the results?
No - there are minor issues

STATISTICS - Is the use of statistics in the manuscript appropriate?
No - there are issues with the statistics in the study

INTERPRETATION - Is the current interpretation/discussion of the results reasonable and not overstated?
Yes - the author's interpretation is reasonable

OVERALL MANUSCRIPT POTENTIAL - Is the current version of this work technically sound? If not, can revisions be made to make the work technically sound?
Probably - with minor revisions

PEER REVIEWER 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. 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.
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. 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 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).

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.

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

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

No

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

Quality of written English
Please indicate the quality of language in the manuscript:
Acceptable

Declaration of competing interests
Please complete a declaration of competing interests, considering the following questions:

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3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

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5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

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