Author’s response to reviews

Title: Effects of Neprilysin-Renin Inhibition in comparison with Neprilysin-Angiotensin Inhibition on the Neurohumoral Changes in Rats with Heart failure

Authors:

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Author’s response to reviews:

Dear Peter Penson,

Thanks for the helpful comments by the reviewers and you, very helpful. I am submitting the revised version of manuscript “Effects of Neprilysin-Renin Inhibition in comparison with Neprilysin-Angiotensin Inhibition on the Neurohumoral Changes in Rats with Heart failure”, which is authored by Kawa Dizaye and Rojgar H. Ali for consideration for publication in BMC Pharmacology and Toxicology.

As per the reviewers comments we edited the texts that were unclear and revised the English language to enhance the comprehension and the flow.

For your information, along with this cover letter, the following files have been submitted:

1. Revised manuscript showing changes through review tracker in MS word.
2. A clean version of the revised manuscripts (no review tracker).
3. Declaration certificate of professional English language editing service
4. Tables file

Additionally, in this letter you will find our one-by-one responses to the reviewer’s questions and comments.

Kind Regards,

Kawa Dizaye
Responses:

1-please state the dose of all drugs in the abstract

Doses of the drugs are added in the abstract (Abstract, page 2, lines 31-32)

2-Please include some quantitative results in the abstract

Some quantitative data were included in the abstract (Abstract, page 2, lines 35-39)

3-Please do not use capital letters for generic drug names or hormones

Capital letters in generic drug names and hormones were all replaced with small letters though out the manuscript, except in the title and beginning of the sentences.

4-In the introduction, I think you could make it clearer that sacubitril is best combined with an ARB/ACEI/Renin inhibitor, because sacubartil will elevate AII

Below paragraph was added in the introduction (Background, page 5 line 92) with a reference:

Since using neprilysin inhibitor alone will increase angiotensin II level, therefore, combining sacubitril with either ACE inhibitors or renin inhibitors could provide further relief of neurohumoral changes associated with heart failure.

5-I'd be interested to know why you didn't use a sacubatril/angiotensin receptor blocker combination

I did not choose angiotensin receptor blocker as it’s already available as combination in the market (entresto) and many similar studies are available in this regard (e.g. Suematsu et al., 2018).


6-Please specify what form ramipril was in when purchased. Tablets? capsules?

It was a tablet, and this information was added (Methods and materials, page 5, line 110).
7-Please state source of Aliskiren

Aliskiren was purchased from a verified pharmacy (Manufactured by Novartis), Source of Aliskiren was added (Methods and materials, page 5, line 110).

8-Please state how exactly sacibitril, aliskiren, ramipril were administered. How could you be sure the whole dose was consumed?

Drugs were administered through oral gavage, and that is after dissolving the medications and calculating exact dose. Below line is added to page 7 line 30 first paragraph In methods section:

Medications were administered though oral gavage after dissolving them in water and calculating exact dose.

9-Please state the route of Xylaxine administration

Xylazine was administered through intraperitoneal injection, and this was added to the methods and materials section (Methods and materials, page 7, line 139).

10-please describe your approach to randomization and blinding of investigators to experimental groups

Simple random sampling method was used and it was added to the manuscript (methods and materials, page 6 line 116).

Serum and urine samples were coded with random numbers to blind the investigators to the samples and avoid biasing. After all the samples have been assessed, the identity of each sample was revealed. This blinding technique was added to the manuscript (methods and materials, page 8, line 148).

11-P7 L 145 - Replace "Turkey" with "Tukey"

"Turkey" was replaced with "Tukey"

12-Please revise your tables. In common with the previous reviewer, I cannot understand what the letters a,b,c mean, and I suspect there is a more conventional way of displaying these data.

I have used a more conventional way to express the statistical differences between expressed data.
13-Your table headings suggest you had ramipril only and aliskiren only groups. Please add "& sacubitril" to both to make this clearer.

“& sacubitril” was added to the other two groups in all tables to make that point clear.

14-Please expand your table legends, so that the tables can be reasonably well understood without reference to the rest of the text. Please state whether values are SEM etc - even if this is repeating information from elsewhere in the manuscript.

Table legends were expanded, values are expressed as mean ± SEM, and this was added to the tables.

14-Discussion Line 216-228 seems to suggest that this is a model of acute cardiac damage. Is this a model of acute injury? long-term failure, or a mixture?

It is both. Heart failure was resulted from the myocardial infarction. Researches demonstrated that administration of isoprenaline induced diffuse myocardial necrosis eventually lead to progressive left ventricular enlargement (e.g. Teerlink et al., 1994).


15-Discussion L 229 - this is unclear, you should state that NTProBNP is a precursor, not a 'product'

Both NT-pro BNP (the inactive N terminal) and BNP (the active part, which is also known as C terminal) are products of proBNP, and I have restated that sentence to be clearer as below:

Both NT-proBNP and BNP are metabolic products of proBNP that is secreted into blood during myocardial stress, and are used as important monitoring tools in the pharmacotherapy of patients suffering from various pathological heart conditions.

16-In addition to your statement relating to the approval of your study by the ethics committee, please state which local/national/international guidelines you were adhering to.

Ethics committee approval was stated in declaration section page 16 line 337.

Throughout this research work we have followed the "Guide for care and use of laboratory animals" provided by National Academy of Science and published by National Institute of Health.
This statement was added in ethics approval part (page 16, line 338-340).