Author’s response to reviews

Title: Abnormal Cisatracurium Pharmacodynamics and Pharmacokinetics among Patients with Severe Aortic Regurgitation during Anesthetic Induction

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1. The second paragraph of the background section discusses the pathology of aortic insufficiency and does not necessarily explain what led to the research project. I suggest deleting this part.

Response: Part of the second paragraph was deleted based on the reviewer’s suggestion.

2. Please better clarify the relevance of the four measures of TOF, knowing that they are separated by 15 seconds and that at T1, TOF=0, theoretically the other measures will also be equal to zero. Also, this data is not presented in the results section and is not discussed later.

Response: The values of T4, T3, T2 and T1 will decrease after muscle relaxants begin to take effect. T4, T3, T2 and T1 will become zero in turn as neuromuscular blockade increases. Finally T1 equals zero when skeletal muscles reach maximal blockade. Therefore, the onset time is defined as the interval between the moment cisatracurium is administered and the moment T1 first reaches zero.

(The revised part in the manuscript was highlighted)
Because the onset time is defined as the interval between the moment cisatracurium is administered and the moment T1 first reaches zero, it’s unnecessary to present the data of T4, T3 and T2 in the result section. The statistical results of onset time were presented in the result section. And the individual onset time of each subject could be provided if needed.

3. If a sample size calculation was not performed, it is desirable to calculate the effect size (r) to estimate whether the sample chosen is appropriate or very small. Also, if there was no sample size calculation, please specify that it is a convenience sample. Please explain why did the authors choose a significant threshold of p at 0.01 (why not at 0.05).

Response: First, we’re sorry we made a typo in the manuscript because we have set the alpha at 0.05 instead of 0.01.

Second, we did a sample size calculation based on our preliminary test data. We did that calculation on a website http://powerandsamplesize.com/Calculators/Compare-2-Means/2-Sample-Equality

We made onset time as the primary endpoint. The alpha was set at 0.05, and the power was set at 0.8. Even a sample size of 3 subjects in each group is sufficient to build the model.

Third, according to suggestion of pharmacologists, generally a sample size of 8 to 12 subjects in each group is adequate to build the same pharmacokinetics model we need. Therefore, 16 subjects in each group are sufficient to build the model and test the group difference in both PD and PK parameters.

4. Table 1 and 2, please specify how the parameters are presented? Mean (SD)? Table 1 and Table 2 could be summarized in the text and deleted. Figures 2 and 3 are also not mandatory. I suggest to only keep Figure 4, adding to means the standardized deviations (column mean/error bars). Figure 5 is also unnecessary.

Response: We’ve changed all the quantitative data into the mean±standard deviation form throughout the manuscript.

Figures 2 and 3 were removed. But we think Tables 1 and 2, Figures 4 and 5 should be retained so as to better illustrate our data.

5. The last paragraph of the discussion could be deleted too. The clinical impact of the study is not major. The study suggests that there is a significant delay of muscle relaxation in patients with aortic insufficiency, but in the presence of a monitoring of the curarization, the practitioner will most likely wait for a deep curarization. I think the importance of the study is to encourage the monitoring of curarization at induction and not to rely on the curare delay in patients with aortic insufficiency.
Response: We agreed to the reviewer’s suggestion that our conclusion should be revised. Here is the revised conclusion section.

In conclusion, this study demonstrated that by PD and PK analysis severe AR impaired distribution of cisatracurium from the central to the peripheral compartment and caused lagged PD responses. These findings underlie the importance of muscular blockade monitoring among patients with severe aortic regurgitation during anesthetic induction.

6. Since aortic regurgitation can also be found in certain other diseases which may come with abnormal pharmacokinetics in patients, I think you should expand the discussion with the benefits of Hoffman degradation compared to other routes of drug metabolism in these patients.

Response: In this study we used cisatracurium, which mainly metabolizes by Hoffman degradation, because we wanted to exclude the disturbances of renal and liver metabolism which may result from differences in patients’ renal and liver function. Drugs, such as rocuronium, are mainly eliminated by the liver and kidney. Therefore, renal and liver dysfunction may cause extension of drug elimination half-life and PD effect. Cisatracurium, which mainly metabolizes in plasma and tissue by Hoffmann degradation, is barely affected by liver and kidney function so it helps us focus on the distribution difference between the AR group and control group. In fact, it’s reasonable to infer that delayed distribution and lagged PD responses of other drugs could be observed among severe AR patients. Therefore, the PD and PK analysis of other drugs are needed and are more challenging since drug elimination will make the analysis more complicated.

Here is the paragraph that will be added to the discussion section

Cisatracurium mainly metabolizes by Hoffmann degradation, which is a spontaneous temperature- and pH-dependent chemical degradation in plasma and tissues. Thus, cisatracurium is barely affected by difference of liver and kidney function among patients so it helps us focus on the drug distribution difference between the two groups and make it easier to find the link between delayed drug distribution and lagged PD response.