Author’s response to reviews

Title: Catecholamine reversal: a case report on unexpected hypotension

Authors:

YOHEI OKADA (okadayohei1127@yahoo.co.jp)
Ryoji Iiduka (iizukar@kyoto2.jrc.or.jp)
Wataru Ishii (wataruaug0804@lily.ocn.ne.jp)
Hiromichi Narumiya (pyroli1117@gmail.com)

Version: 2 Date: 04 Mar 2017

Author’s response to reviews:

Dr. Michael Kidd, Flinders University, Australia

Editor-in-Chief

Dear, Editor

Please find attached a revised version of our manuscript entitled “Catecholamine reversal: a case report on unexpected hypotension” (JMCR-D-16-00780R1), which we would like to resubmit as a Case Report in Journal of Medical Case Reports.

We would like to thank the reviewer for the careful and constructive comments.

We have carefully considered the comments and have revised the manuscript accordingly. Our responses to each of the comments are given below in a point-by-point manner. We hope the revised version of the manuscript and our accompanying responses will be sufficient to make our manuscript suitable for publication.

Thank you.
For the Reviewer #2

Thank you for your constructive comment. We response to each comments and revised our manuscript according to your comment.

1. On the original review comments, I have requested the vital signs which include heart rate, blood pressure, respiratory rate, capillary refill time, body temperature and urine output. Since you have his cardiac output, cardiac index and SVR measurements, it would be helpful to list them as well on a daily basis. Please complete them by making a table.

Response:

Thank you for your good advice. Respiratory rate and body temperature on admission was added in the manuscript. However the record about his cardiac output, cardiac index, SVR, and CVP in the ICU were lost unfortunately, because these were not recorded in the electronic medical chart, but in the paper chart. We are sorry that we could not revise my manuscript according in response to your request.

2. If your patient was clinically stable on day 2, what hesitated you to transfer him to the general ward up to day 5 of his care? This was unanswered from the previous comment. Please elaborate.

Response: On day 2, after the extubation, he was transferred to general ward from the ICU, and on day 5, he was transferred from the general ward to the psychiatric ward for the psychiatric care. We added the information in the manuscript.

3. You mentioned that continuous hemofiltration was performed due to his metabolic acidosis and elevated lactate level, please list his serial lactate level and upon what basis was hemofiltration terminated?

Response:

Thank you for your good suggestion. We added the lactate and the reason why we terminated the hemofiltration.
4. Here are the comments on some of the references that you listed:

a). Reference #2 reported on the use of BOTH alpha and beta blockade and the concomitant use of adrenaline. In your case, risperidone is reported to have an alpha blocking effect; NONE on beta-1 nor beta-2 receptors. Therefore, if noradrenaline and dopamine works by binding strongly to alpha-1 receptors with minimal effect on beta-1 and almost negligible effect on beta-2 receptors, how can it cause unopposed stimulation through B2 vasodilatory effect?

Response:

In reference #2, it is written, “adrenaline reversal is invariably linked with the extent of B2-adrenoceptor stimulation, and is explicable solely as a phenomenon of a-adrenoceptor blockade unveiling a B2 –action which intrinsically exceeds the corresponding B1-effect.” Therefore, we understand that this reference may support our idea that a-blockade effect by risperidone might have cause the hypotension due to the emphasis on B2 effect.

Yes, adrenaline does have a high affinity for beta-2 receptors and have been known to contribute to hypotension; however, how do you explain the possible mechanism of noradrenaline in causing hypotension? It would be helpful to elaborate more on the proposed mechanism by which ‘Noradrenaline’ may cause hypotension through published reports from other papers/research.

Response:

In reference #5, it is written “noradrenaline dilates the blood vessels of the splanchnic region during blockade of alpha-receptors”. Thus, we believe that this report may support our statement.

b). Reference #4 is a report of antipsychotic overdose and even recommends the use of norepinephrine for hypotension, based on the drugs mechanism of action. There are multiple reports on risperidone overdose with an ingested dose ranging from 1mg-240mg, and their reported side effects. Perhaps it might be true that concomitant noradrenaline usage with alpha blockade may cause unexpected hypotension. Please find the supporting evidence.

Response:

In reference #5, it is written “noradrenaline dilates the blood vessels of the splanchnic region during blockade of alpha-receptors”. Thus, we believe that this report may support our statement.
c). Reference #7 is a report on hypotension and beta-1 blockade using carvedilol. This reference is not applicable for your case report which solely acts on alpha blockade, due to risperidone. It has no effect on beta blockade; hence, the use of dobutamine in your case would not cause unopposed B2 stimulation which may have caused the hypotension.

Response: Thank you for your suggestion. I agree with you, and I deleted the reference #7 and the sentence about it in the manuscript.

d). Reference #8 is a paper on specific molecular models of receptors and how to improve their binding affinity. Can you elaborate on how this evidence supports your statement on hypotension during dobutamine infusion and beta-blockade?

Response: Thank you for your suggestion. I agree with your idea that this reference #8 doesn’t support my statement. I deleted #8 and the sentence about it in the manuscript.

Overall, this paper may bring light to the possibility that noradrenaline may have caused refractory hypotension through mechanisms that you still need to explore. I suggest you review and revise the content of your paper. Multiple journals have published several cases of risperidone and antipsychotic agents overdose alongside its management; hence this is not the first case on refractory hypotension due to effects on alpha blockade. The references are too few with some being outdated as far back as 1964 and based on small scale animal models. Additionally, it would be helpful if this case report was written in a flowing and eloquent manner instead of reporting information piece by piece.

Response:

Thank you for your understanding that our report may show the possibility that noradrenaline may have caused refractory hypotension. We understand that there are some papers about the risperidone overdose. However, in our report, we intended to highlight not the side effect of the risperidone overdose, but the interaction between catecholamine and risperidone, because cardiovascular effects by risperidone overdose are rare, according to the references you suggest. To best our knowledge, unexpected hypotension due to catecholamine infusion with alpha-blockade is clinically described in only one case (our reference #4).

Moreover, “adrenaline reversal” is a well-known phenomenon described in a lot of pharmacology textbook, however, it is only based on the animal experiments. Therefore, we believe that this report may be educational for clinicians.
Thank you again for your understanding.

Here are some of the references that I came across while searching for risperidone overdose:


Response:

Thank you for your good advice.

Reference#1 suggested by the reviewer has already mentioned in the manuscript as the reference #6. However, Reference#2, and 3 suggested by the reviewer shows that the risperidone overdose rarely causes the severe hypotension, and the hypotension in our case is caused by not only risperidone overdose but also another mechanism. Thank you again.