Author’s response to reviews

Title: A case report of clonidine induced syncope: a review of central actions of an old cardiovascular drug

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Author’s response to reviews:

We appreciate the opportunity to have our case report reviewed. We are particularly thankful for the time the peer reviewers put into reading the report and providing feedback. We have amended the report per the recommendations of the reviewers and provide a step-by-step response to each point made below:

Reviewer 1: The manuscript entitled "A case report of bradycardia induced syncope: central actions of an old cardiovascular drug" (PHAT-D-17-00007) describes the case of a 69 yr old diabetic patient who was on a polypharmacy regimen including clonidine, and fainted at a parking lot. He was found bradycardic at the ER and his bradycardia resolved after clonidine discontinuation. The authors discuss this clinical case in the context of preclinical evidence from the literature suggesting new mechanisms for clonidine-induced bradycardia such as the disinhibition of vagal neurons in the brainstem. While I do agree with the authors that a reminder on side effects of clonidine and an update on its pharmacological effects could be timely because clinicians are starting to be less aware about old drugs that are, however, still used in the clinical practice, I would recommend to address the following points to make the paper more appealing and straightforward.

-1. In the present version of the manuscript, the aim of the study is unclear: are the authors just presenting a case report that they believe to be interesting, are they writing a short review on clonidine side effect, or they want to give clinically relevant information for physicians who prescribe antihypertensive drugs? The only mention of an aim is at the end of the first paragraph of the discussion (row 23, page 2 of the manuscript). Please reformulate the Introduction to make clear what the objectives of the study are.
We address points 1 and 2 together below.

-2. I would suggest a more conservative title such as "Bradycardic effect of clonidine: a case report and a literature review" or, maybe, "Bradycardic effect of clonidine: a case report and an update on pharmacodynamic mechanisms". The present title is, indeed, misleading because it raises the expectations for some kind of experimental procedure performed to determine the site of pharmacological action whereas the authors just discussed new evidence from the literature.

Thank you for bringing up the clarity of the purpose for the article. Indeed, the purpose is to use this case report as a vehicle to discuss recent research into the pharmacological effects of clonidine to further educate and remind physicians the importance of its actions. We have included this intention in the introductory paragraph and have also updated the title of the case report to better reflect the purpose. It is now “A case report of bradycardia induced syncope: a review of central actions of an old cardiovascular drug.” We believe this better reflects the intentions and makes clear what a reader should expect.

-3. As stated by the authors, it is not unexpected that clonidine could lower heart rate. It is well known that bradycardia can occur in clonidine intoxication or in specific clinical applications such as in anesthesia. However, what practitioners probably would like to know is how often this could be a problem in patients taking clonidine for the chronic treatment of hypertension. According to Golusinski and Blount (1995) the risk should be very low (in the field of case reports, indeed!). Could the authors update Golusinski and Blount (1995) information and make a systematic search in the literature to come out with an estimate of the risk of bradycardia? This could be helpful.

We appreciate this comment and completely agree with the desire to have data on incidence of clonidine toxicity. Unfortunately, there has not been a study to date that provides data on the incidence of clonidine toxicity. Even the Golusinski and Blount report (1995) in Journal of Family Practice doesn’t provide statistics on incidence of clonidine toxicity, but rather highlights particular risk factors for developing toxicity. They also suggest mechanisms of clonidine induced toxicity which allows us to essentially update their contribution from that standpoint.

-4. Assuming that the risk is low it would be important at least to speculate on why the patient did develop this complication: the authors should clearly state whether the patient was taking clonidine since a long time or he started the drug from a few days. Did the authors evaluate the possibility that their diabetic patient was affected by CAN (cardiac autonomic neuropathy)? It would be interesting to discuss whether undiagnosed CAN that per se increases the risk of
bradycardia in diabetic patients, could represent a risk factor for clonidine-induced bradycardia. In addition, even though the drugs taken by the patient are not known to potentiate clonidine heart effects, the authors should explicitly discuss the point of polypharmacy and potential drug interactions in an elderly patient like the one whose story is addressed in the paper.

This is a great point, and yes, we did consider other possibilities in the differential including complications due to diabetes. We have included that now in the text which is highlighted at the end of the case, before the discussion.

-5. From a clinical practice point of view, it could be important to mention that clonidine is in the Beers list of dangerous drugs in the elderly.

This certainly makes the report more applicable to a wide variety of clinicians, so we have now included this in the introduction; thank you for this suggestion.

-6. Just to go back to a point briefly mentioned before, personally I found the discussion not fitting with the case report: unless the authors state already in the title that the aim is to write a pharmacology review and, therefore, the case report is just functional to exemplify the relevance of the problem, the discussion should first be focused on the specific patient (see points 3 and 4) and then, briefly, move to the pharmacological mechanisms. Alternatively, the analysis on pharmacological mechanisms could better fit in the introduction.

Again, a great point brought up by the reviewer on the intentions of the report. We think updating the title (above) helps clarify this point.

Reviewer 2: A case of a syncopal event with bradycardia is presented. The Authors link these symptoms with clonidine. However, this connection does not seem to be supported sufficiently in the text.

The patient takes several drugs, and some of them, especially when they are administrated together, could cause bradycardia as well, for example, amlodipine/clonidine+lisinopril (PMID: 20852161, 26075111, http://www.shmabstracts.com/abstract/a-case-of-symptomatic-bradycardia-from-amlodipine/).
Syncope and dizziness could also be due to hypoglycemia caused by insulin + lisinopril or insulin+clonidine combination, and other. These and other hypotheses should be discussed, and the explanation for the decision for clonidine discontinuation should be given.

This is an important point the reviewer brings up, especially in the academic arena it is important to include other etiologies on the differential. We have now included the possibility of polypharmacy in the case, highlighted at the end. Additionally, there was a high degree of suspicion that the clonidine was responsible early on, since the patient had started it 1.5 years prior and started having the symptoms for the past year. This is reflected in the text now and highlighted.

Potential reasons for symptoms presentation should be given. I assume patient takes all the drugs for a long time, so why he is symptomatic for several months only?

We have clarified in the text how long the patient had been on the clonidine and the congruence with the onset of symptoms. Thank you for this comment.

When the patient's bradycardia resolved is also of interest.

We have included in the text, now highlighted in the case in the second to last paragraph, that the bradycardia resolved after 2-3 days. This is also in the figure.

The unusualness of the report should be stated clearly, as bradycardia is known to be a complication of clonidine therapy (PMID: 7472189, 28107093).

The citation here is a great addition to the literature and was not available to us at the time of our submission. It is now included as an important source describing clonidine overdose as uncommon, albeit a well-known complication of clonidine (but possibly not always classified as overdose). We have included this in the first paragraph of the discussion.

Minor:
- Reported blood pressure values lack units
- Abbreviations should be explained at first use
- References are not formatted in compliance with BMC Pharmacology and Toxicology requirements

We have added units, non-universally-known abbreviations, and reformatted citations.

Sincerely,

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