**Reviewer's report**

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

**Version:** 0 **Date:** 20 Jan 2017

**Reviewer:** Mauro Cataldi

**Reviewer's report:**

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.

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.

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.
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.

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.

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.

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

Yes

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

Unable to assess

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?
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