Author's response to reviews

Title: Patients presenting with metoprolol-induced visual hallucinations: a case series

Authors:

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Version: 5 Date: 8 December 2011

Author's response to reviews: see over
Dear Reviewers:

I want to thank you for your feedback and constructive criticism related to the submission of my article for publication in the Journal of Medical Case Reports. Your help was appreciated for the improvements to the content and format of the article. Hopefully I have addressed your concerns and made the necessary changes. I have highlighted the changes in yellow so they would be easier to visualize in the revised manuscript and I outlined them below.

Reviewer's report
Title: Metoprolol-induced visual hallucinations: a case series
Version: 2 Date: 11 November 2011
Reviewer: Milos Dobias
Which of the following following best describes what type of case report this is?: Unreported or unusual side effects or adverse interactions involving medications
Has the case been reported coherently?: Yes
Is the case report authentic?: Yes
Is the case report ethical?: Yes
Is there any missing information that you think must be added before publication?: No
Is this case worth reporting?: Yes
Is the case report persuasive?: Yes
Does the case report have explanatory value?: Yes
Does the case report have diagnostic value?: Yes
Will the case report make a difference to clinical practice?: Yes
Is the anonymity of the patient protected?: Yes
Comments to authors:
I have only a small remark to the manuscript sentence ( Patients with hallucinations related to metoprolol may tolerate a switch to a more hydrophilic beta-blocker such as atenolol ).
I think that switch metoprolol to atenolol only depends on the base of drug indication and patient's diagnosis. In the case i.e. of chronic heart failure isn’t atenolol drug of choice. In case of heart failure a more hydrophilic beta-blocker such as bisoprolol is indicated. Only beta-blockers whose efficacy has been demonstrated in large scale clinical trials should be used in the treatment of chronic heart failure, i.e. bisoprolol, carvedilol, metoprolol (succinate) and nebivolol.

I think this is an excellent criticism. As all the patients in the case series had either hypertension or coronary artery disease, I did not think to include those with CHF. I expanded the discussion section to include other diagnosis and the third generation beta blockers.

**Quality of written English:** Acceptable

**Declaration of competing interests:**
I declare that I have no competing interests

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**Reviewer's report**

**Title:** Metoprolol-induced visual hallucinations: a case series

**Version:** 2  **Date:** 18 October 2011

**Reviewer:** James Paul Johnston

Which of the following following best describes what type of case report this is?: Unreported or unusual side effects or adverse interactions involving medications

Has the case been reported coherently?: Yes

Is the case report authentic?: Yes

Is the case report ethical?: Yes

Is there any missing information that you think must be added before publication?: Yes

Is this case worth reporting?: Yes

Is the case report persuasive?: Yes

Does the case report have explanatory value?: Yes

Does the case report have diagnostic value?: No

Will the case report make a difference to clinical practice?: Yes

Is the anonymity of the patient protected?: Yes

**Comments to authors:**

I feel that the case reports need to be standardised slightly such as in the first case report a list is given of other medication. This has not been repeated in the subsequent cases. I would also like to know a time scale if possible over which the symptoms began following starting the metoprolol initially. Perhaps a table or comment about other commonly prescribed beta blockers now used such as nebivolol, carvedilol and the lipophilicity of each. Are there case reports about these newer agents?
The case reports have been standardized to include a chronic medication list. I also included a time line that hopefully clarified when the visual hallucinations started as related to the start of metoprolol when it could be ascertained. In the discussion section, I included comment about the third generation beta blockers and their lipophilicity. There have been no case reports about the newer agents causing visual hallucinations and I included comment about that as well. This was an excellent comment.

I standardized the case presentations to include a list of medications

Quality of written English: Acceptable

Declaration of competing interests:
I declare that i have no competing interests.

Reviewer's report
Title: Metoprolol-induced visual hallucinations: a case series
Version: 2 Date: 1 November 2011
Reviewer: Louise Pilote
Which of the following following best describes what type of case report this is?: Unreported or unusual side effects or adverse interactions involving medications
Is the case report authentic?: Yes
Is the case report ethical?: Yes
Is there any missing information that you think must be added before publication?: Yes
Comments to authors:
General comments:
This is a very interesting case series of suspected metoprolol induced visual hallucinations. It is pertinent to report series such as this one because of the esoteric nature of the side effect and the frequency of use of the drug in question. While the improvement of symptoms with discontinuation of metoprolol certainly points to it being the likeliest cause, I feel that the descriptions of the cases do not thoroughly explain the investigations, if any, which were done to rule out other etiologies of visual hallucinations (metabolic causes, neurodegenerative conditions). If metoprolol indeed is the cause, it has to be considered a diagnosis of exclusion and this was not evident in the case summaries.

Revisions necessary for publication:
A more detailed description of pertinent aspects of the history, physical examination and laboratory/imaging assessment of the patients is necessary in order to ensure that all other organic diagnoses are entertained and ruled out. Some aspects of the suspected metoprolol induced hallucinations differ from those previously reported, such as the long delay between initial prescription of metoprolol and the adverse effect in question. There was no effort to explain why
this occurred. Moreover, each of the cases presented with nocturnal hallucinations. Is there a hypothesis as to why they only occurred at night? Has the case been reported coherently? Yes, though more detail pertaining to the case history would be beneficial as would hypotheses as to why the adverse event took so long to appear and why there was a particular time of day in which the adverse event occurred.

I included pertinent details of the history/physical exam and neurological work up for the case presentations. Case 1 had a full work up performed which was negative. The visual hallucinations resolved after the metoprolol was discontinued. A full neurologic work up was not performed with either Case 2 or 3 as the visual hallucinations were consistent with prior reports of CNS side effects of beta blockers and resolved after discontinuation of metoprolol. It was decided not to pursue further work up for these patients that had resolution of their symptoms.

The long delay in diagnosis was related to physician ignorance (including my own), and patient reluctance to report this side effect due to potential ridicule. Revisions to the manuscript included clarification and emphasis on this. Prior reports included the acute onset of delirium associated with the hallucinations which was not evident in our patients but most likely made the CNS side effects more visible to others earlier in these reports. The cause of beta blocker induced nocturnal hallucinations is still unclear although I included several proposed possibilities as etiologies. Another good criticism.

Is there any missing information that you think must be added before publication?
- Yes
More detail in the case presentations to rule out other organic causes of hallucinations. The author should offer hypotheses as to why it took so long to develop the adverse event and why the adverse event was solely nocturnal.

Is this case worth reporting?
- Yes x
- No
Given the popularity of metoprolol and the fact that alternatives exists, highlighting a rare yet reversible adverse affect of the medication is worthwhile.

Is the case report persuasive?
- Yes x
- No
As a frequent prescriber of metoprolol, I'd be interested in learning about such an adverse effect.

Does the case report have explanatory value?
- Yes
The author does not attempt to explain the lag time between starting the medication and the onset of symptoms. Moreover, the author does not attempt to explain why the symptoms are nocturnal.

Please see above

Does the case report have diagnostic value?
-------------------------------------------
- Yes
- No x

Will the case report make a difference to clinical practice?
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- Yes x
- No

If physicians are aware of this side effect, they are more likely to question patients. If patients respond affirmatively, there are alternative medications to replace metoprolol if needed.

Is the anonymity of the patient protected?
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- Yes x
- No

**Quality of written English:** Acceptable

**Declaration of competing interests:**
I declare that I have no competing interests

The Associate Editor who is handling your manuscript would like to pass on the following comments:

'I would recommend the authors to focus mainly on the following points in their revised version of the manuscript:

1. Standardization of the case reports description - provide a full list of chronic medication in each case.
Manuscript revised as per recommendations

2. Please provide a time scale of symptoms following metoprolol application. It would be useful for the readers to draw up a graph showing this time scale.

Manuscript revised as per recommendations. Time line put in each case presentation when possible.

3. State if there was any investigation performed to rule out other possible causes of hallucinations.

Manuscript was revised per recommendations. The first case underwent a full neurological investigation with resolution of her symptoms once the metoprolol was discontinued. Case 2 and 3 had visual hallucinations consistent with CNS side effects of beta blockers and their metoprolol was discontinued with resolution of their visual changes. Work up was thus not pursued with patients that had resolutions of their symptoms.

4. Discuss a switch to atenolol and beta-blocker prescription in the chronic heart failure

Changes were added to the manuscript

In addition, the editorial team would like to request for formatting changes required for your manuscript, as it does not conform to the journal's style. Kindly address the following:

- Please reformat the study design in your title, i.e. Case series. For example: A presenting with B in C: a case series

Title was changed as per format style

- Please include patients' ethnicity in the abstract and case presentation sections.

Changes made to manuscript

- Please number the case presentation section from Case 1 to 3. Eg: Case 1; Case 2 and Case 3
Changes made to manuscript

My drive for publishing this case series is to bring to light a side effect of a very commonly prescribed beta blocker. Since I have seen three cases in the last 18 years, I believe that this occurs more frequently than we realize. Patient reluctance to report hallucinations and physician ignorance (including my own) to this side effect of metoprolol worsen the problem. Only with healthcare provider education can we hope to make a difference with recognition of visual hallucinations related to metoprolol.

Thank you again for your assistance.

Sincerely,

Jonathan A. Goldner, DO, FCCP, FCCM