Author’s response to reviews

Title: Complete Atrioventricular Block due to Timolol Eye Drops: A Case Report and Literature Review

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Version: 2 Date: 21 Oct 2019

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Point-by-point Response Letter to Reviewers

We would like to thank the Reviewers for their thoughtful and insightful comments regarding the manuscript. Our responses to the reviewer’s comments are listed below in the order that they appear in the original review. Additional new information added to the revised manuscript is denoted by an underline.

Reviewer 1

1. I am missing use of a causality assessment method such as Naranjo.

Response: The Naranjo scale is scored in the Table 1S in Supplement Material. We got a total score of 6, it is a probable ADR. The statement is added in Discussion (page 7, paragraph 2, line 1-3).

2. Please add what kind of treatment the patient received after discontinuation of the suspected drug.
Response: After Timolol was discontinued, Travoprost was given to decrease ocular pressure. Isoprenaline infusion was continued, but the dose was decreased gradually when HR increased, and stopped when HR recovered to 45-60 bpm at 24-hour after the discontinuation of Timolol. The administration of hydrochlorothiazide was continued. One week later, when the patient was discharged, Irbesartan was added together with hydrochlorothiazide to treat hypertension. A sentence was added to the Case Presentation (page 5, paragraph 1, line 7-11) to clarify the drug use after the discontinuation of timolol.

3. I think causality grading will be possible rather than probable in face of lacking previous ECG data.

Response: Please see the answer in question 1. Because the total score is 6, it belongs to a probable ADR.

4. Was the drug company and regulatory authorities informed? Please add some few words.

Response: This case was reported to the State Food and Drug Administration Adverse Event Reporting System, which is the regulatory authority in China. It was not reported to the drug company, due to lack of existing reporting system in this company. This statement is added to the very end of Case Presentation (page 6, paragraph 1, line 1-5).

Reviewer 2

1. Overall, it is important to underline the novelty of this case report, both in the abstract and in the text (discussion and conclusion), especially in comparison with literature data (see below).

Response: The case presented in this report has the longest latent period, 13 years, compared with literature, until timolol induced AV block was symptomatic and detected. Considering the first-degree A-V block appeared again after a one-year discontinuation of timolol, we reason the patient had a subclinical preexisting conduction defect, that was uncovered and exacerbated by timolol use. We think both timolol and the existing conduction defect synergistically contributed to the complete A-V block in this case. This statement has been added to the discussion (page 8, paragraph 2, line 15-18, and page 9, paragraph 1, line 1). A part of abstract has been rewritten to show to novelty of this case report (page 2, paragraph 1, line 4-6). The longest latency and has been addressed in discussion (page 8, paragraph 2, line 1-11, and Table 1).

2. The title implies that literature review was undertaken, but this issue appears to be only marginally addressed in the text. It is unclear how (search strategy) and where (MEDLINE?) literature review was carried out. The reader might appreciate a table summarizing collected evidence from literature in order to fully understand the unusual
aspect of this case report (the manuscript just quoted "some research suggest"... and "the longest latency according to literature").

Response: We searched literature on PubMed and Google Scholar. We added a summarizing Table 1 in Discussion to list the information in several other case reports (page 8, paragraph 2, line 3-5).

3. I agree that the drug might have triggered the AV block in a patient with underlying conduction defect (independent on timolol). The unclear aspect is that the patient recovered (increased heart rate) after 48 h from timolol discontinuation. The authors should discuss whether this timeline is in line with pharmacokinetics and pharmacodynamics of timolol. For instance, It might be that the drug had accumulated because of impaired metabolism and/or reduced elimination. Because renal/liver function were apparently normal, the issue of genetics should be discussed in more detail as a plausible mechanism (poor metabolizer).

Response: We think the patient has a first-degree A-V block as his cardiac conduction defect. However, timolol is responsible for transforming the first-degree A-V block to a third-degree A-V block. So, the underlying conduction defect and timolol both contribute to the complete A-V block. The pharmacokinetics and pharmacodynamics analysis of the systemic effects of topical timolol demonstrated that the onset of action is in 20-30 min, with a peak effect at 4 hours, and a half-life of 4-5 hours, and duration of action about 24 hours.11 In the current case, the recovery time was 48 hours, which was markedly longer than its pharmacokinetics would suggest. This could be explained by the possibility that this patient is a CYP2D6 slow metabolizer, which would cause timolol to accumulate in the circulation and take longer to be metabolized. Another speculation is that this patient is 62 years old, and the elimination of timolol in an elderly adult is much slower than that in a healthy young adult.12 This paragraph has been added to the Discussion (page 7, paragraph 2, line 4-15).

4. In order to assess causality, the authors should consider to apply recognized algorithms such as Naranjo and WHO.

Response: Please see the answer to question 1 of reviewer 1. The Naranjo grading was shown in Table 1S. This case belongs to a probable ADR. Using the WHO-UMC causality evaluation, we still think this is a case of probable/likely ADR (page 7, paragraph 2, line 3-4). The reasons are listed below:

1) EKG showed complete A-V block; and 15 minutes after timolol topical use, third-degree A-V block reappeared;

2) The third-degree A-V block is not attribute to any other disease nor drugs

3) Forty-eight hours after the discontinuation of timolol, the third-degree A-V block attenuated to first-degree A-V block
5. The authors should consider to place ECG figures as supplementary material. Conversely, for a reader, it would be useful to have an explanatory figure providing the timeline of events.

Response: ECG figures are placed in the supplement material file. The timeline of events is shown in Figure 1 at the end of Case Presentation (page 6, paragraph1, line 4-5).