

Response to Review Comments

(Manuscript Number: 79716)

I am very much thankful to the reviewers for their deep and thorough review. I have revised my present case report in the light of their useful suggestions and comments. I hope my revision has improved the paper to a level of their satisfaction. Number wise answers to their specific comments/suggestions/queries are as follows.

Response to Reviewer #1 Comments

Comment 1: The relationships between the mode of administration, dose and time of amiodarone and the occurrence of muscle tremor are not clearly described. It is not clear in the manuscript that when the neurology consultation was requested and when the patient started to take levetiracetam. How long does the patient start to recover the lower limb function after taking the medicine, and when does it return to normal? For these reasons, a timetable or a timeline is recommended.

Response: Respected reviewer thank you for your comments. According to your suggestion, We added the patient's **timeline**.

- Aug.9 08:56[↵]
ECG suggests paroxysmal supraventricular tachycardia[↵]
- Aug.9 09:20[↵]
Amiodarone injection 150mg intravenously, not cardioverted[↵]
- Aug.9 09:42[↵]
Amiodarone 1 mg/min continuous intravenously[↵]
- Aug.10 08:20[↵]
The patient presents with lower extremity tremors[↵]
- Aug.10 08:30[↵]
Calcium gluconate injection 1mg intravenously[↵]
- Aug.10 10:00[↵]
Amiodarone 0.5mg/min continuous intravenously[↵]
- Aug.10 13:00[↵]
If tremor persists, discontinue amiodarone[↵]
- Aug.10 13:05[↵]
Propafenone injection 70mg IV to restore sinus rhythm[↵]
- Aug.10 14:00[↵]
Neurology Consultation[↵]
- Aug.10 14:30[↵]
Levetiracetam 250mg bid[↵]
- Aug.10 21:00[↵]
The tremor has eased[↵]
- Aug.17 08:00[↵]
Complete tremor relief[↵]

Comment 2: The description of the muscle tremor can be more detailed, such as the type of muscle tremor, frequency, duration, specific location, aggravation and relief methods.

Response: Modified according to your suggestions, At 08:20 on Aug.10, the patient started to have lower extremity gastrocnemius tremor, accompanied by pain (muscle fiber necrosis) at a frequency of about 6 Hz. The patient was given an intravenous injection of calcium gluconate 1 mg, the symptoms were not mitigated significantly, the tremor symptoms persisted, and the tremor occurred after lower extremity activity It was aggravated and mitigated slightly after rest, but the tremor still persisted. (page3 line19-24)

Comment 3: “The next morning, the patient began to experience involuntary lower limb gastrocnemius pain with muscle tremors. (Page 3, Line 18-20)”. Involuntary muscle tremors are usually without pain. Please describe this part in detail. Please explain the cause and differential diagnosis of the muscle pain.

Response: ①Muscle injury is considered as the cause of muscle pain; ②The differential diagnosis is described on page6 line26 page7 line10

Comment 4: The discussion section is a little brief; for example, it can be expanded the mechanisms of the central nervous system.

Response: The discussion section has been expanded according to your suggestions

Comment 5: Please describe how does “desethylamiodarone (Page 7, Line 28)” relate to muscle tremors?

Response: desethylamiodarone contain separate hydrophilic and hydrophobic structures, are capable of interacting with anionic groups of membrane phospholipids, neutralizing the charge of phosphate groups and displacing calcium ions. The above changes may result in necrosis of muscle fibers and muscle tremors in patients. (page6 line7-12)

Comments 6: Please explain how does “lysosomal phospholipid”(Page 1, Line 1) relate to muscle tremors?

Response: perineural cells to form lysosomal phospholipid complexes, thus resulting in increased pH inside lysosomes and inhibition of lysosomal enzymes, which interfere with lysosomal protein degradation. Autophagic vacuoles were formed, and muscle biopsy showed the features of necrotizing myopathy and vacuolar myopathy, with disorganized muscle fibers, and the patient showed peripheral neurological symptoms (e.g., muscle twitching and muscle weakness). (page6 line15-21)

Comments 7: I suggest removing the sentence “We combined the patient’s previous medical history, medication, medication after admission, relevant tests, and examinations to make a differential diagnosis. (Page 8, Line 3-5)” for its redundancy.

Response: According to your suggestion, we deleted this sentence.

Comments 8: Please discuss how does “autophagic vacuoles (Page 8, Line 20) ” relate to muscle tremors?

Response: Similar to the Comments 5 and Comments 6, muscle biopsy showed the features of necrotizing myopathy and vacuolar myopathy, with disorganized muscle fibers, and the patient showed peripheral neurological symptoms (e.g., muscle twitching and muscle weakness).

Comments 9: Please report the drug dose range of amiodarone-induced muscle tremor and its correlation with age according to relevant references in the discussion section.

Response: The dose of amiodarone-induced muscle tremor remains unclear. Amiodarone-induced hypothyroidism, renal insufficiency, concomitant use of statins, and age all significantly increase the incidence of toxic neuromyopathy (page 6 line 21-24)

Comments 10: How to use amiodarone reasonably and standardized to avoid adverse reactions in the treatment of arrhythmia in elderly patients according to relevant references?

Response: When elderly patients are administrated with amiodarone, cardiologists and pharmacists should carefully evaluate the long-term and short-term side effects, as well as whether combined use with other drugs will increase the adverse reactions of amiodarone. Changes in the patient's condition should be closely observed, and if there are signs of adverse reactions, immediate intervention (e.g., changing the drug or reducing the dose of the drug) should be performed to reduce the adverse reactions of amiodarone. (page 8 line 9-15)

Comments 11: Please remove “Lower limb” in the sentence “Lower limb muscle tremor is a movement disorder characterized by...”. (Page 9, Line 1)

Response: According to your suggestion, we deleted this sentence.

Comments 12: I suggest rewriting the conclusion of the abstract for the lack of accuracy in summarizing the conclusion of this manuscript.

Response: Attention should be paid to the significance of the side effects of drugs in the elderly, which may be atypical in the elderly. The relevant side effects of drugs may not be as

rare as reported due to individual differences and different pharmacokinetics. If the side effects are generated, the medication should be adjusted in time, and the progress of the side effects should be intervened. (page1 line 23)

Comments 13: Considering the right of privacy, please remove the patient's personal information in the figures.

Response: The patient's personal information was deleted according to your comments.

Comments 14: Please do not use Chinese in the figure.

Response: Revised according to your comments.

Response to Reviewer #2 Comments

Comment 1: Dear Authors, Thank you for submitting your manuscript, entitled, "Amiodarone-Induced Muscle Tremor in an Elderly Patient: A Rare Case Report" in WJCC. The manuscript is well written and simply summarized and readable. However, some major criticisms should be addressed as the following. 1) Please add new references because the number of references is too small. For instance, when searching amiodarone, adverse reaction, tremor as keywords in Pubmed, the following 8 manuscripts were hit. 1: Stahlmann R, Lode H. Safety considerations of fluoroquinolones in the elderly: an update. *Drugs Aging*. 2010 Mar 1;27(3):193-209. 2: Stahlmann R, Lode H. Fluoroquinolones in the elderly: safety considerations. *Drugs Aging*. 2003;20(4):289-302. 3: Hilleman D, Miller MA, Parker R, Doering P, Pieper JA. Optimal management of amiodarone therapy: efficacy and side effects. *Pharmacotherapy*. 1998 Nov- Dec;18(6 Pt 2):138S-145S. 4: Orr CF, Ahlskog JE. Frequency, characteristics, and risk factors for amiodarone neurotoxicity. *Arch Neurol*. 2009 Jul;66(7):865-9. 5: Bongard V, Marc D, Philippe V, Jean-Louis M, Maryse LM. Incidence rate of adverse drug reactions during long-term follow-up of patients newly treated with amiodarone. *Am J Ther*. 2006 Jul-Aug;13(4):315-9. 6: Palakurthy PR, Iyer V, Meckler RJ. Unusual neurotoxicity associated with

amiodarone therapy. Arch Intern Med. 1987 May;147(5):881-4. 7: Morady F, Sauve MJ, Malone P, Shen EN, Schwartz AB, Bhandari A, Keung E, Sung RJ, Scheinman MM. Long-term efficacy and toxicity of high-dose amiodarone therapy for ventricular tachycardia or ventricular fibrillation. Am J Cardiol. 1983 Nov 1;52(8):975-9. 8: Coulter DM, Edwards IR, Savage RL. Survey of neurological problems with amiodarone in the New Zealand Intensive Medicines Monitoring Programme. N Z Med J. 1990 Mar 14;103(885):98-100.

Response: Respected reviewer thank you very much for your valuable suggestions. Your suggestions made a huge improvement in our research paper. The references were updated according to your opinions, but the first and second references you gave were about fluoroquinolones. Did you send them incorrectly? For other References, I have made appropriate choices. Thank you very much.

Comment 2: Are tremor-like adverse reactions from amiodarone really rare? 44 case of tremor patients has been reported in the following manuscript. Palakurthy PR, Iyer V, Meckler RJ. Unusual neurotoxicity associated with amiodarone therapy. Arch Intern Med. 1987 May;147(5):881-4. “The most frequent neurotoxic findings were tremor (44 patients), peripheral neuropathy (ten patients), and ataxia (seven patients).”

Response: There are very few reports of such severe tremor in the video I submitted.

Comment 3: Please add new table summarizing the reported cases to date, while summarizing each item of year, reporter, name of journal, age, gender, primary disease, amiodarone administration method and dosage, course of treatment for primary disease, timing of appearance of side effects, and outcome. Furthermore, please add new considerations and discussions from the new table. What can you say from that new table? Add to the conclusion.

Response: Reference 7 summarized some cases of Mayo Clinic in the past, with a similar structure

ROUND 2

Response to Review Comments

(Manuscript Number: 79716)

Thank you for your letter and for the reviewers' comments on our manuscript entitled "Amiodarone-Induced Muscle Tremor in an Elderly Patient: A Case Report" (ID: 79716). All of these comments were very helpful for revising and improving our paper. We have studied these comments carefully and have made corresponding corrections that we hope will meet with your approval. [The changes in the revised manuscript are marked in red.

ROUND 2

Response to Reviewer

Comment 1: Please add new table summarizing the reported cases to date, while summarizing each item of year, reporter, name of journal, age, gender, primary disease, amiodarone administration method and dosage, course of treatment for primary disease, timing of appearance of side effects, and outcome. Furthermore, please add new considerations and discussions from the new table. What can you say from that new table? Add to the conclusion.

Response: There are five reports related to amiodarone induced muscle tremor on PubMed, one of which reported two cases of amiodarone induced muscle tremor, for a total of six patients, and we summarize their data in Figure 5, from which we can find that the median age of these patients at the onset of muscle tremor was 63.5 years (range 41-87), the median dose of amiodarone was 400 mg /d (range 200 -600), the median duration of taking amiodarone at the onset of symptoms was 2 months (range 2-10), the patients were instructed to discontinue amiodarone, two of them were given levetiracetam and the other four simply discontinued amiodarone, and

the patients were closely observed for changes in their condition, and the final result was that the muscle tremor symptoms were effectively relieved in all six patients.

	reporter	name of journal	Age and gender	primary disease	amiodarone administration method	dosage timing of appearance of side effects	course of treatment for primary disease	timing of appearance of side effects	outcome
1	Michael Mark Stanton	BMJ Case Rep	87-year female	Atrial fibrillation	Oral administration	600 mg/day	3 months	2 months	Tremor improved
2	Diego Celli	HeartRhythm Case Rep	60-year male	Ventricular tachycardia	Oral administration	200 mg/day	3 years	4 months	Tremor improved
3	Ken-ichi Uehi	JAPANESE CIRCULATION JOURNAL	41-year male	Ventricular tachycardia	Oral administration	400 mg/day	6 years	10 months	Symptoms completely relieved
4	E P Flanagan	Eur J Neurol	67-year male	Atrial tachycardia	Oral administration	400 mg/day	unknown	2 months	Symptoms completely relieved
5	E P Flanagan	Eur J Neurol	76-year male	Atrial fibrillation	Oral administration	200 mg/day	unknown	2 months	Symptoms completely relieved
6	A. Arnaud	La Revue de Médecine Interne	45-year male	Ventricular tachycardia	Oral administration	400 mg/day	unknown	2 months	Symptoms completely relieved

Fig. 5: Summary of case data on amiodarone induced muscle tremor.

Kind regards,
Xiao-Yong Zhu