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Title: Paliperidone palmitate-induced facial angioedema: A case report

Dear Professor Lian-Sheng Ma,
Company Editor-in-Chief,

We would like to express sincere gratitude to you, the reviewers, and the editorial office for the very helpful constructive comments. We have made revision and improved our case report in response to the reviewers and the editorial office' comments and hope that this revised version will make a good contribution of knowledge. The important changes are highlighted. With the revised manuscript submitted, we respond to the reviewers and editorial office' comments as following:

Reviewer # 1

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: The title, abstract, introduction, language etcetera are ok. For further comments see the attached file.

(Attached file) The case is well-presented. Different options are discussed and the conclusions are adequate. However, the indications to medicate with Donepezil and thereafter with an antipsychotic are somewhat obscure. A well-known side effect associated with Donepezil is hallucinations, agitation and aggressivity and discontinuation with this medication may have solved the problem, perhaps making antipsychotics avoidable. Furthermore, the exact diagnosis should have been given so the reader could evaluate the need for the medications given. This does however not argue against the association between paliperidone palmitate and angioedema found by the authors. If the associations are dose dependent, then this may explain why injectables with a proneness to give higher blood-concentrations a couple of weeks after administration give higher risk for the edema side effect as compared with oral administration with a more stable and fairly low concentration. This possibility may have been discussed.

Response: From the reviewer's attached file, we have answered and corrected our case report, as follows:

1. Which one? Paliperidone should be given to patients with psychoses only?

Response: We have corrected the word "major neurocognitive disorder" to "major neurocognitive disorder due to Alzheimer's disease" throughout the paper for clarification. Thank you for your suggestion. We also have corrected the sentence to the Abstract section, Case summary, at lines 2-3, as follows: "Paliperidone palmitate was off-label used to control her aggression, irritability, and psychosis."

2. To date this is an off-label indication.

Response: We have corrected a sentence in the Introduction section at line 6, as follows: "Moreover, in patients with major neurocognitive disorders, it has been used off-label to control neuropsychiatric symptoms..."

3. It depends on which antipsychotic it is compared with. For instance the partial agonists have fewer side effects.

Response: We have added the sentence to the end of the Introduction section at lines 7-9, as follows: "Paliperidone palmitate can also prevent relapse of schizophrenia as effective as fluphenazine decanoate while carrying a lower risk of tardive dyskinesia and anticholinergics use."

4. Very low numbers such as 1-5 are usually spelled out (i.e. two)

Response: We have corrected the sentence in the History of Present Illness section at lines 2, as follows: "A retired teacher living with two daughters."

5. Her hallucinations might be a side effect of donepezil, o why not reduce or abolish this medication.

Response: We added the following sentence to the History of Present Illness section at lines 9-12: "Her primary doctor believed that the patient's psychiatric symptoms were explained by the progression of Alzheimer's disease rather than donepezil-induced hallucination because donepezil had been constantly given at low dose (5 mg/day) for one year."

6. Curious, since the drug is the main active metabolite of risperidone.

Response: We have added sentences to the 4th paragraph of the Discussion section at lines 16-21, as follows: "We hypothesized that increasing dose might be a key factor in developing angioedema in this patient because angioedema did not occur when oral paliperidone 6 mg (equivalent to paliperidone palmitate injection 75 mg)^[14] or risperidone 2 mg (equivalent to paliperidone palmitate injection 50 mg)^[21] were

given, but developed at higher dose of paliperidone palmitate injection 150 mg and 100 mg.”

Reviewer # 2

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: Dear authors, I have a few comments on your manuscript: - You keep the patient’s diagnosis top secret. The diagnosis "a major neurocognitive disorder" is very vague. Would you kindly more specify the diagnosis (e.g. Alzheimer’s disease, vascular dementia etc.)? - You write that the patient was originally treated with risperidone and quetiapine. Was it in the form of pills or a solution? - In "Physical examination" you write "Both lungs were clear". Do you mean auscultation or radiological examination? The reviewer

Response: We have corrected the word “major neurocognitive disorder” to “major neurocognitive disorder due to Alzheimer’s disease” throughout the paper for clarification. Thank you for your suggestion.

We have corrected the word in the History of Present Illness section to “oral risperidone” at line 12 and “oral quetiapine” at lines 14 and 17.

We have corrected the sentence in Physical Examination section at line 5, and now reads: “Both lungs were clear on auscultation.”

Editorial office’s comments

(1) Science editor:

1 Scientific quality: The manuscript describes a case report of the paliperidone palmitate-induced facial angioedema. The topic is within the scope of the WJCC. (1) Classification: Grade B and Grade C; (2) Summary of the Peer-Review Report: The title, abstract, introduction, language etcetera are ok. The questions raised by the reviewers should be answered; and (3) Format: There are 1 table and 1 figure. A total of 21 references are cited, including 1 references published in the last 3 years. There are no self-citations.

2 Language evaluation: Classification: Grade A and Grade B. A language editing certificate issued by a native English speaker was provided.

3 Academic norms and rules: The authors provided the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement, and the written informed

consent. No academic misconduct was found in the CrossCheck detection and Bing search.

4 Supplementary comments: This is an unsolicited manuscript. No financial support was obtained for the study. The topic has not previously been published in the WJCC.

5 Issues raised: (1) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

6 Re-Review: Required.

7 Recommendation: Conditional acceptance.

Response: We thank the Science editor for helpful comments. We have provided the original pictures with text descriptions in PowerPoint file.

(2) Editorial office director: I have checked the comments written by the science editor.

Response: We thank the Editorial office director.

(3) Company editor-in-chief: I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Clinical Cases, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

Response: We thank the Company editor-in-chief.

Again, we are deeply appreciated the reviewers, the Science editor, and the Editorial office director that made us revise this case report to its best. We welcome any additional advice or comments. Thank you so much for the time and wisdom that have put into this paper in the very details.

Yours sincerely,

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