

Peer Review File

Article information: <https://dx.doi.org/10.21037/apm-23-581>

Reviewer A

Thank you very much for reviewing our manuscript and providing valuable comments. We appreciate for the time and energy you expended. Our responses to your comments are as follows:

Comment 1: There is no mention of the possibility that increased blood levels of not only oxycodone but also oxymorphone may have caused respiratory depression. It is unfortunate that no blood samples were taken, as the only way to distinguish which was more affected was to look at blood levels.

Reply 1: It is as you pointed out. We have cited the literature you provided and added it to my discussion. We have noted that we were unable to measure blood levels as a point of reflection.

Changes in the text: We added the sentences (see Page 7, lines 119-122 and Page 8, lines 148-151).

Comment 2: Line 45, Was the fentanyl ceased?

Reply 2: Yes, fentanyl was switched to oxycodone after rehospitalization.

Changes in the text: We added the sentence (see Page 5, lines 87-89).

Comment 3: Can Figure 1 also include the respiration rate?

Reply 3: We added respiration rate in the Figure 1.

Changes in the text: We changed the Figure 1 (see Figure 1).

Comment 4: The patient required multiple bolus of oxycodone, why not use an infusion?

Reply 4: We used continuous infusion of oxycodone, but the patient still needed rescue bolus doses multiple times. The continuous dosage was gradually increased while monitoring the number of rescues.

Changes in the text: We added the explanation (see Page 5, lines 87-89). We also changed the word “injection” to “infusion” throughout the text.

Comment 5: Confirm that the antiemetics were all IV administration.

Reply 5: Yes, all of the antiemetics were administered intravenously.

Changes in the text: We added the word “intravenously” (see Page 6, line 94).

Comment 6: Was the patient receiving any other medications (e.g. neuropathic pain), not listed including over the counter or herbal medicines?

Reply 6: No, such medications have not been administered to the patient.

Changes in the text: We added the sentences (see Page 5, lines 84-85 and Page 7, lines 122-123)

Reviewer B

Thank you very much for reviewing our manuscript and providing valuable comments. You pointed out a lot of things that we hadn't noticed, and we learned a lot from them. We appreciate for the time and energy you expended. Our responses to your comments are as follows:

Comment 1: In the abstract, we may need to indicate which CYP isoenzyme activity is specifically inhibited by aprepitant, and we may also need to mention whether aprepitant is a CYP competitive or non-competitive inhibitor, as well as whether aprepitant is considered a strong, moderate, or weak inhibitor.

Reply 1: As you pointed out, we added this information in the abstract.

Changes in the text: We added the information (see Page 2, lines 30 and 32)

Comment 2: In the introduction, we would better consider briefly explaining the various mechanisms potentially involved opioid-related drug interactions. Also, we failed to mention the CYP metabolic pathway of oxycodone.

Reply 2: We agree exactly what you pointed out. We added the sentences based on the explanations you provided in the Discussion section and added only the explanation of the CYP metabolic pathway of oxycodone in the Introduction section.

Changes in the text: We added the sentences in the Introduction and Discussion (see Page 4, lines 59-60 and Page 7, lines 119-124).

Comment 3: In the case description, can we provide any information about the patient's kidney function?

Reply 3: We are sorry, but we didn't take this into consideration even though it is very important information for drug metabolism. The patient had decreased renal function throughout his hospitalization. We added data to main text.

Changes in the text: We added the information in the case description (see Page 5, lines 74-76).

Comment 4: In the discussion, we need to point out that the patient was administered an antiemetic "cocktail" composed of three different drugs, including aprepitant.

Reply 4: It's exactly as you pointed out. We have added more detailed information about antiemetics.

Changes in the text: We added the sentences (see Page 7, lines 122-129).

Comment 5: We need to explain the metabolism of oxycodone and its proposed interaction with aprepitant in more detail.

Reply 5: As you pointed out, we think it would be easier for readers to understand if there was such an explanation. We added the explanation in the text as you suggested.

Changes in the text: We added the sentences (see Page 7, lines 119-124).

Comment 6: We need to discuss about the kidney function as potentially contributing factor for respiratory depression in this patient.

Reply 6: As you pointed out, this patient had decreased renal function, which we believe had a considerable influence on this event. We added the sentences about renal function.

Changes in the text: We added the sentences about contribution of renal dysfunction (see Page 8, lines 136-139).

Comment 7: We need to discuss about how we ruled out dexamethasone and palonosetron as potentially offending drugs in this case.

Reply 7: As you pointed out, we were intentionally focusing only on aprepitant, not excluding dexamethasone or palonosetron. We believe that the potential interaction between oxycodone and dexamethasone or palonosetron should also have been considered. We added the sentences regarding the possibility that three antiemetics may have influenced this event and that aprepitant is most likely related to this event.

Changes in the text: We added the sentences (see Page 7, lines 122-129).

Comment 8: Discussion about reference #8 by Fujiwara et al. needs to be reconsidered. Caution should be taken when considering that oxycodone is generally safe to use in combination with aprepitant without changing the dosage based on this literature alone.

Reply 8: As you pointed out, when citing this reference #8, we should have discussed it more critically in comparison with the present event. We changed the discussion as you suggested.

Changes in the text: We added the sentences (see Page 8, lines 144-148).

Reviewer C

Thank you very much for reviewing our manuscript and providing valuable comments. We are thankful for the time and energy you expended. Our responses to your comments are as follows:

Comment 1: There are several potential drug interactions that may be contributing to the adverse events in this patient, all of which should be discussed on this manuscript. Dexamethasone or palonosetron may also have contributed to the present event, thus it is unreasonable to attribute this event to aprepitant alone. We need major revision in addition to changing the title of this manuscript.

Reply 1: As you pointed out, similar points have been made by other reviewers. We were intentionally focusing only on aprepitant. We believe that the potential interaction between oxycodone and dexamethasone or palonosetron should also have been considered. Thank you for the valuable information. We are sorry, but unfortunately, we couldn't find any mention of palonosetron being a CYP3A4 inhibitor. We added the discussion about three antiemetics. And we changed the title of this manuscript as "Opioid-induced respiratory depression suspected of drug interaction in a prostate cancer patient: A case report".

Changes in the text: We added the sentences (see Page 7, lines 122-129).

Comment 2: Needs more thorough demographic data.

Reply 2: We added the information in the case description.

Changes in the text: We added some information (see Page 5, lines 73-76).

Comment 3: Clarification is needed regarding if the patient had been on other medications during this hospitalization.

Reply 3: No other medications have been administered.

Changes in the text: We added the sentences (see Page 5, lines 84-85 and Page 7, lines 122-123)

Comment 4: Both the word “aprepitant” and “fosaprepitant” appeared in the text. We need to unify the word.

Reply 4: After explaining the metabolism of fosaprepitant, we unified the terminology to aprepitant.

Changes in the text: We added the explanation (see Page 6, lines 94-95).

Comment 5: The statement about morphine and hydromorphone is inaccurate and needs to be corrected.

Reply 5: We are sorry, but we didn't think about the minor metabolic pathways. We deleted this sentence.

Reviewer D

Thank you very much for reviewing our manuscript and providing valuable comments. We appreciate for the time and energy you expended. Our responses to your comments are as follows:

Comment 1: The title of this manuscript should be changed to be more informative.

Reply 1: We have revised the content of the main text and changed the title to “Opioid-induced respiratory depression suspected of drug interaction in a prostate cancer patient: A case report”.

Comment 2: The use of the tool published by Horn, JR et al. is strongly recommended.

Reply 2: Thank you so much for sharing the tools to assess drug interactions. We use the tool and mention about it in the text.

Changes in the text: We added the sentence (see Page 7, lines 117-118).

Comment 3: Why are the anticancer drugs infused 3h after antiemetics?

Reply 3: We thought so too. As you pointed out, anticancer drugs are usually administered immediately after antiemetics. We think the gap was probably due to hydration infusions, etc. The pharmacist said that considering the half-life of antiemetics, there would be no problem even if the interval is extended by about 3 hours.

Comment 4: Was the anticancer treatment planned only D1?

Reply 4: As you pointed out, etoposide was administered D2 and D3. But fosaprepitant and palonosetron were administered only on the D1, which is determined and recommended in Japan, and only dexamethasone was administered on the D1 to D3. Respiratory depression did not occur on the D2 and D3. This may mean that even if antiemetics were involved, dexamethasone was not.

Changes in the text: We added the sentence (see Page 6, lines 104-105).

Comment 5: Remove the sentence in Page 3, lines 81-82.

Reply 5: We have deleted the sentence as you pointed out.

Comment 6: Remove “in July of year X” in Page 3, line 90.

Reply 6: We have deleted the words as you pointed out.

Comment 7: Replace “suppressed” by “inhibited”

Reply 7: We have replaced the word as you pointed out.

Comment 8: Disagree with the hypothesis in Page 4, line 154.

Reply 8: The pain itself was reduced by the effects of radiation therapy, and it was already time to reduce the dose of oxycodone, but we continued the same dose resulting in an overdose. We hypothesized that antiemetics may have inhibited the metabolism of oxycodone in this condition,

and as a result, blood levels may have risen above acceptable levels. We have changed the text to make it easier to understand.

Changes in the text: We added the sentences (see Page 7, line 132-Page 8, line 135).

Comment 9: The authors should take a look a recent abstract presented at ESMO conference.

Reply 9: Thank you for providing us with very helpful materials. We have revised the text using this abstract as a reference.