Author's response to reviews

Title: Tacrolimus toxicity from tibolone co-administration: a case report

Authors:

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Author's response to reviews: see over
To the Editor,
The Journal of Medical Case Reports

Dear Sir,

Re: MS 1815604660336746
Tacrolimus toxicity from tibolone co-administration: a case report
Carolyn J Clark, Carmel M Hawley and David W Mudge

Thank you for reviewing our manuscript. We have addressed the concerns of Reviewer 2 and have made the necessary changes as listed below. The changes have been incorporated into a revised version which we are now submitting for further consideration.

Responses to Reviewer:

- Page 1. Title: Since this is a “probable” interaction I would recommend changing the title to: “Probable Tacrolimus Toxicity Co-administration: A Case Report”

Response: We agree. The title has been changed as suggested.


Response: We are unsure as to exactly what the reviewer is referring to here. In the abstract we do not refer to, or quantify the magnitude of the tacrolimus concentration increase as far as we are aware. Nor could we find such a reference on adjacent pages. Could the reviewer clarify this issue?

- Page 3. Introduction: There needs to be a transition between comments regarding tibolone and the statement of your case. Perhaps the tie in should be the incidence of osteoporosis in kidney transplant recipients and the use of agents such as tibolone.

Response: We are grateful for this suggestion, and have added the sentence “Steroid-induced osteoporosis remains a significant problem in solid-organ transplantation, and it is likely that HRT will continue to be utilised for the prevention of osteoporosis in these patients.” to the middle of the introduction paragraph as a tie-in.

- Page 4. Case report. Second paragraph. The authors mention that the only change to her medications was tibolone but in the paragraph above the patient was taking cyclosporine at some time and was switched to tacrolimus. On her presentation, I would provide all of the medications with doses and her allergies to medications for completions. At our institution, most of our kidney transplant recipients are on a statin and/or a blood pressure medication, which she wasn’t receiving.

Response: We agree that all of the other medications should be listed in a drug-interaction case report and have added them in as suggested. (lower paragraph, page
4). We have also made some minor changes on page 4 to clarify the time-course of the medications used.

- Page 4. Case report. Second paragraph. Please provide all baseline labs (serum glucose and creatinine specifically) and baseline tac levels. Please provide tac doses.

*Response:* We have added these results as suggested (page 5).

- Page 6. Conclusions. Based on your case, how often should tac concentrations be monitored? Should the dose of tac be cut initially as is done when adding diltiazem.

*Response:* We have attempted to answer these questions. Because of the genetic variability of metabolism of drugs via the P450 pathway, we would suggest that some (but not all) patients are susceptible to this drug interaction. Recommendations about dose reductions are difficult, therefore, because this would expose the majority of patients to underdosing and the risk of rejection. Our suggestion is therefore to use therapeutic drug monitoring on day 3 to assess whether there has been a significant rise in the tacrolimus level. This should be early enough to allow a dose reduction and avoidance of significant toxicity in patients with a significant interaction. We have added the sentences “However, given pharmacogenetic variability, not all patients would be expected to be affected” and “…and should ensure monitoring of tacrolimus concentration within 3 days of commencement of tibolone. Prophylactic dose reduction of tacrolimus is not advised, as it is not likely that all patients will be affected.” to the discussion to attempt to answer these questions.

Thank you for considering these responses to the Reviewer, and for further review of our revised manuscript.

Yours Sincerely,

David Mudge
On behalf of the authors.