Author's response to reviews

Title: Optimising plasma levels of clozapine during metabolic interactions: a review and case report with adjunct rifampicin treatment.

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Author's response to reviews:

Dear Editors,

We are very grateful to Drs. Pai, Chetty, Gramaglia and Salvi for their time in reviewing our manuscript. We have responded to their helpful comments in the following manner:

• Typographical errors identified by reviewers have been corrected
• Inaccuracies identified by Drs. Chetty and Salvi in the Background section have been corrected
• We have further reviewed the literature concerning the interaction between rifampicin and psychotropic medication and added 3 paragraphs describing this data to the Background section
• We have expanded on the limitations of interpretation of the plasma concentration data as suggested by Dr. Chetty in the Discussion section
• A reference has been added describing the role of absorption difficulties in abdominal TB in relation to this case report has been added to the Discussion section
• Further exploration of the role of other interacting medications has been added to the Discussion section
• We apologise that the figures have no captions – as they are JPEG images we cannot add these, but they should be:
  • Figure 1. Clozapine metabolic pathway
  • Figure 2. Temporal relationship between clozapine plasma concentration, dose, and concurrent medication
• We have altered the abstract to avoid giving the impression that this is the only case report in this area, as suggested by Dr. Gramaglia
• Regrettably we feel unable to shorten the introduction further as requested by Dr. Gramaglia due to the requests for additional material made by other
reviewers

• We agree with Dr. Salvi that information about the clinical presentation of the patient during the fluctuations in clozapine plasma level is essential. We also agree that this is best presented by use of recognised rating scales. Unfortunately these were not completed at the time and so this is not possible. This is also the case for rating scales related to mood disorders. We have instead added descriptive narrative to the report regarding clinical presentation.

• We note Dr. Salvi’s point that rifampicin may also have reduced plasma levels of lamotrigine, possibly also causing a worsening in mental state. The patient was being prescribed a slow increasing titration of lamotrigine during the time course of the rifampicin treatment. Plasma levels correspondingly increased over time. We apologise that this wasn't made clear in the original report and have now clarified this in the discussion, and noted the interaction in the introduction.

Yours faithfully,

Siobhan Gee (on behalf of the authors)