Author’s response to reviews

Title: Successful treatment of a schizophrenic patient with phenotypic evidence for CYP2D6 ultrarapid metaboliser status and non-response to amisulpride with melperone-augmented haloperidole: a case report

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Author’s response to reviews: see over
Dear Editor,

thank you for your friendly electronic mail from October 20th 2011 and the favourable overall assessment of our manuscript made by the referees. We also appreciate their valuable suggestions for further improving the paper.

We have carefully considered all suggestions made by you and the reviewers and have revised the manuscript accordingly. All changes in the manuscript are highlighted with bold letters.

In the following, we will respond to the referees’ comments on an item-by-item basis.

Referee #1 (Salih Selek):

We thank the referee for the positive assessment and the suggestions made for further improving the paper:

1. The title has been changed accordingly to “Successful treatment of a patient with schizophrenia and phenotypic evidence for CYP2D6 ultrarapid metabolizer status and non-response to amisulpride with melperone-augmented haloperidole”. In addition, the term “schizophrenic” was changed throughout the manuscript to “patient with schizophrenia”.
2. We agree with the referee’s statement of existing literature that provides treatment recommendations. But, in contrast, evidence based guidelines for patients with schizophrenia, CYP2D6 UM status and non-response to amisulpride are missing. With our report we primarily want to contribute to the set of available experience with this particular treatment situation. Creating true evidence based guidelines requires a sufficient pool of data, to which...
we contribute with our report. In order to avoid the misunderstanding that is stated by the referee we changed the term “treatment recommendations” to “evidence based guidelines” in the abstract, introduction and discussion section.

3. The core message of our report was limited in order to avoid generalisation, as suggested by the referee, in the abstract and discussion section.

4. Key word was changed accordingly.

5. The introduction section was rewritten accordingly. Augmentation is now explained more clearly and the paragraph that deals with fluvoxamine-augmentation of clozapine was deleted completely due to its insignificant contribution.

6. We already handled this point under our second point.

7. We thank the referee for his advice. The manuscript has now been corrected by a native speaker. Typos and grammatical errors are now eliminated.

8. We now added more clinical information an explained the course of diagnosing the schizophrenia at this patient.

9. Quetiapine was tapered of due to its missing antipsychotic effect in this patient after one week of reliable oral intake of 700mg/day. Increase of its dosage was not performed against the background of sufficient quetiapine serum levels. This circumstance is now stated more clearly in the case presentation section.

10. We mentioned the metformine treatment in order give a complete overview of the patient´s medication. The indication of metformine is now explained in detail (metabolic syndrome).

11. In this point we do not agree with the referee´s opinion. 21 days of treatment with a comparatively high dose of amisulpride (1200mg/day) that was titrated up to this dose within 5 days, without clinical success, seems to be a sufficient interval to judge this treatment as ineffective.

12. Unfortunately we did not use rating scales. Evaluations were made based on the clinical impression of three psychiatrists that were involved in the patient’s treatment over the whole period of time. The criterion was the reduction of psychotic symptoms (auditory hallucinations) and disorganized speech and behaviour. These aspects remained unchanged during amisulpride treatment.

13. Haloperidole decanoate was administered in a dose of 150 mg, risperidone was given orally up to 8 mg per day. The missing doses have been added.

14. The procedure of phenotypical testing for CYP2D6 metabolizer status is now explained in detail in the case presentation section.

15. As stated in the text, trazodone was administered for augmentation of haloperidole. Trazodone is a common CYP2D6 inhibitor and thus a possible agent for augmentation of haloperidole (in order to increase haloperidole serum levels with unchanged haloperidole dosage). Since the treatment with amisulpride (that is eliminated on a renal pathway) failed we did not try other antipsychotics.

16. We wanted to call attention to the circumstance that in our case haloperidole plasma levels increased after escalation of haloperidole dosage and simultaneous add-on therapy with melperone. Thus, it is not clear to what content melperone really contributed to the elevation of haloperidole serum levels. To prove an essential involvement of melperone (relevant CYP2D6 inhibition) discontinuation of melperone and repeated measurements of haloperidole serum levels (without melprone) should have been performed. Since the intractable clinical situation was stable under treatment with haloperidole and melperone for the first time we refrained from discontinuation of melperone in order to avoid relapse. In order to clarify this we reformulated the respective paragraph.

17. We already cited two studies in the discussion section (reference number 5 and 6). In the conclusion we now make a connection between these studies and our clinical observations.
Referee #2 (Erman Bagcioglu):

We thank the referee for his favourable overall assessment of our manuscript. Though the reviewer indicated missing information within the evaluation matrix he did not elucidate this. Thereby, we hope that the changes that were made based on the comments of referee#1 are sufficient.

We again thank the referees for the helpful comments, hope that the changes now qualify the manuscript for publication in the *Journal of Medical Case Reports*, and look forward to hearing from you.

Yours sincerely,

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