Successful treatment of schizophrenia with melperone augmentation in a patient with phenotypic CYP2D6 ultrarapid metabolism: a case report

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Abstract

Introduction: There are limited treatment options for people with schizophrenia with cytochrome P450 2D6 ultrarapid metabolizer status who do not respond to amisulpride. Furthermore, the literature does not provide evidence-based guidelines for this particular constellation.

Case presentation: We report the case of a 50-year-old Caucasian female patient with schizophrenia and cytochrome P450 2D6 ultrarapid metabolizer status who experienced an insufficient antipsychotic effect with amisulpride. She was successfully treated with melperone-augmented haloperidol.

Conclusion: This report yields melperone-augmented haloperidol as a possible pharmacological strategy in the described situation. In addition, our observations support the available evidence for the potential of melperone to act as an inhibitor of cytochrome P450 2D6.

Introduction

Enhancing the effect of a pharmacological agent by adding on another drug is commonly called augmentation. One possible augmentation strategy is via induction of pharmacokinetic interactions. Here the added agent interacts with enzymes of the cytochrome P450 system (CYP) that is important for the hepatic metabolism of numerous drugs. Thus, utilizing the pharmacokinetic properties of a particular agent allows its application as a specific inhibitor or inductor of metabolic pathways of the drug to be enhanced. This can, for example, allow decreased doses to result in sufficient plasma level concentrations. Within the CYP family, CYP2D6 is a poly-morphic enzyme that is of relevance for the metabolism of most typical antipsychotics [1]. There are more than 100 genetic variants (catalogued by the website: http://www.cypalleles.ki.se). Out of these, there are four phenotypes (poor, intermediate, extensive and ultrarapid metabolizers) that are associated with different enzyme activities and whose incidence vary among ethnic groups [2]. Ultrarapid metabolizers (UM) are people with markedly elevated enzyme activity; there are estimated to be between 0.5% and 7% UMs within the Caucasian population [3,4]. Patients with intractable schizophrenia and CYP2D6 UM status can benefit from a treatment with the antipsychotic amisulpride, which is almost completely eliminated through the renal pathway. Therapeutic alternatives for non-responders under amisulpride are limited and evidence-based guidelines regarding this particular treatment situation are lacking. In the following, we report successful treatment with melperone-augmented haloperidol in a patient with schizophrenia and UM status.

Case presentation

Our patient was a 50-year-old Caucasian woman, a non-smoker, with a 20-year history of undifferentiated schizophrenia, according to the Diagnostic and Statistical Manual, Fourth Edition, Text Revision criteria. She was admitted to our clinic for acute psychotic exacerbation. Due to numerous treatments in our clinic over the last 10 years, our patient was well known and the diagnosis of schizophrenia was confirmed by our clinic.

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schizophrenia had been secured based on several psychot- 
ic episodes and unremarkable somatic examination, 
including analysis of her cerebrospinal fluid, an electro- 
encephalogram and magnetic resonance imaging of her 
brain.

Initially, she presented with auditory hallucinations, dis- 
organized speech, inappropriate affect with an occasionally 
euphoric mood, grossly disorganized behavior and excit- 
ability. Prior to this hospital admission, her antipsychotic 
treatment (retard preparation of quetiapine, 700 mg per 
day) was taken irregularly. Further, impaired glucose toler- 
dance due to adiposity and metabolic syndrome (weight 
102.8 kg, height 156 cm, body mass index 42.2 kg/m²) was 
treated with metformin (500 mg per day). We first contin-
ued quetiapine for seven days without amelioration of the 
clinical situation. In view of sufficient quetiapine serum 
levels (854 ng/mL) and remarkable obesity, a treatment 
trial with an increased dosage of quetiapine was not per-
formed. While tapering off quetiapine, we administered 
amicusulpride and titrated up to a daily dosage of 1200 mg 
within five days. No substantial improvement was achieved 
with this regimen within 21 days.

Phenotypic testing in our patient with dextromethoro-
phan (DM) revealed CYP2D6 UM status (DM < 5 ng/mL; 
dextrotofran (DO) 640 ng/mL; DM/DO ratio: < 0.008; 
3-methoxymorphan (MM) < 5 ng/mL; 3-hydroxymor-
phan (HM) 24 ng/mL; MM/HM ratio: 0.21), which also 
explained recent ineffective treatment attempts with ris-
peridone (up to 8 mg per day) and haloperidol-decanoate 
(up to 150 mg per injection). This phenotypic testing was 
performed by taking a blood sample (120 mL) exactly one 
hour after the oral application of 40 mL NeoTussan® 
cough syrup (111 mg dextromethorphan per 100 g sus-
pension (Novartis Consumer Health GmbH; city: Munich; 
state: Bavaria; country: Germany). Her blood was analyzed 
for metabolites of DM and MM, which are substrates of 
CYP2D6. The DM to DO and MM to HM ratios are sur-
rogate parameters for CYP2D6 activity.

Following the reduction of amisulpride down to 800 mg 
per day, haloperidol (10 mg per day) was applied as an 
additional antipsychotic. Simultaneously, trazodone (100 
mg per day) was added on in order to augment the hal-
operidol by CYP2D6 inhibition, but did not show significant 
clinical success in the next days. Gradual escalation of 
haloperidol and trazodone doses over a period of one 
month did not obtain amelioration of the psychotic phe-
nomena. At that time, haloperidol plasma levels (current 
medication: amisulpride 800 mg per day; haloperidol 
15 mg per day; trazodone 200 mg per day; and metformin 
500 mg per day) were at 10 ng/mL. A subsequent increase 
of haloperidol up to 20 mg per day did neither improve 
the clinical situation nor serum plasma levels (9 ng/mL).

Since her psychopathological findings did not change 
under treatment with amisulpride and still presented as on 
admission time, the antipsychotic effect of amisulpride was 
evaluated to be insufficient according to the treatment 
guideline for schizophrenia of the German Association for 
Psychiatry, Psychotherapy and Neuroscience [5]. After dis-
continuation of trazodone and amisulpride, we adminis-
tered melperone (100 mg per day), in order to inhibit 
CYP2D6, and elevated haloperidol up to 30 mg per day. 
After 14 days, her haloperidol plasma levels were at 19 ng/
/mL. This result was confirmed in a second test (haloperi-
dol: 20 ng/mL). In line with this, her clinical performance 
proved slightly, and she demonstrated attenuation in 
her auditory hallucinations, redevelopment of day struc-
ture and a marked improvement regarding behavior and 
speech. Our patient was then discharged with this medica-
tion in a clearly improved clinical condition.

Discussion

There are no evidence-based guidelines in the literature 
for patients with schizophrenia and CYP2D6 UM status 
that do not respond to amisulpride. Our report yields 
the combination of a high dose of haloperidol augment-
ed with melperone as a possible pharmacological strat-
egy in patients under these conditions. Considering that 
the patient’s haloperidol serum levels increased concur-
tently with elevated doses of haloperidol, the question 
arises to what the melperone effectively contributed to 
sufficient haloperidol serum levels. Though reports on 
the potential of melperone as an inhibitor of CYP2D6-
dependent metabolization of psychopharmacologic 
drugs are available [6,7], it is conceivable that, in our 
case, sufficient haloperidol plasma levels were simply a 
consequence of escalated oral haloperidol doses, and to 
a lesser extent induced by melperone-mediated CYP2D6 
inhibition. Discontinuation of melperone and repeated 
measurements of haloperidol serum levels under the 
removed influence of melperone could have provided 
clarity. However, due to the unstable clinical situation 
and first-time treatment success with melperone-aug-
mented haloperidol, we refrained from any modification 
of the psychopharmacotherapy. Apart from that, the 
combination of haloperidol and melperone was success-
ful in our patient with regard to haloperidol plasma 
levels and schizophrenic target symptoms. Retrospec-
tively, the repeated modifications of psychopharma-
cotherapy in this case during a comparatively short 
period of time are problematic and thus, for example, 
continuation of amisulpride for a longer interval should 
have been attempted.

Conclusion

We hypothesize that melperone-augmented haloperidol 
can be considered as a possible treatment strategy in 
patients with schizophrenia, CYP2D6 UM status and 
insufficient antipsychotic effect of amisulpride.
Furthermore, our observation of sufficient haloperidol plasma levels under augmentation with melperone is in line with studies that described melperone as an inhibitor of CYP2D6-dependent metabolization of risperidone [6] and venlafaxine [7].

Consent
Written informed consent was obtained from the patient’s legal guardian for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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Authors’ contributions
MG wrote the manuscript. RG, MMK and CSL were involved in the patient’s treatment and investigation of data. RWF was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

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