

# A case of a schizophrenic patient with unusual pharmacogenetics profile

## Abstract

There are plenty of evidences supporting the contribution of genetic variability to the mechanisms that responsible for both therapeutic and adverse effects of antipsychotic medications. We report a case that is an example of using cytochrome P450 pharmacogenetics and therapeutic drug monitoring in an attempt to guide schizophrenia treatment. This example illustrates the potential of applying the principles of predictive, preventive, and personalized medicine to the therapy of psychotic disorders.

**Keywords:** schizophrenia, pharmacogenetics, therapeutic drug monitoring, antipsychotic drugs, genetic variability

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**Abbreviations:** AP, antipsychotic drugs; TDM, therapeutic drug monitoring; PGx, pharmacogenetics; MRM, multiple reaction monitoring; DNA, deoxyribonucleic acid; CYP, cytochrome P450; PCR, polymerase chain reaction; CLO, clozapine; QUE, quetiapine; NOR, norclozapine; ARI, aripiprazole; DHA, dehydroaripiprazole; MHRC, mental health research center

## Introduction

Antipsychotic drugs (AP) are widely prescribed for the treatment of major psychiatric illness. Unfortunately, many prescribed medications are not effective for certain individuals or can cause serious adverse effects. Information gathered from pharmacogenetic testing and therapeutic drug monitoring (TDM) can allow clinicians to predict a patient's propensity for medication response and risk for adverse drug reactions. Utilizing this information, a treatment plan can be customized for a certain patient to improve treatment outcomes.<sup>1</sup> On the other hand, case reports are a time-honored, important, integral, and accepted part of the medical literature.<sup>2</sup> Here, we describe a case of a subject with an unusual profile of pharmacogenetics (PGx). The plasma concentration of the AP was detected using liquid tandem chromatomass-spectrometry.<sup>3</sup> Target compounds were extracted from plasma using liquid-liquid extraction (methyl-tretbutyl ether) under alkaline conditions. To determine the AP and their active metabolites, a triple quadrupole mass spectrometer was used in the mode of determining the given masses (+MRM) under conditions of electrospray ionization. For genotyping DNA was extracted using phenol-chloroform. The single cytochrome P450 (CYP) polymorphisms were genotyped after PCR according to standard protocols using an amplifier Real-Time PCR System (StepOnePlus, Applied Biosystems) and blind to the clinical status of the participants.<sup>4</sup>

## Case report

The patient anonymized as PKG86 is a 24-year-old Russian male with a rather long history of mental disorders with the onset in his teens. His medical background includes a traumatic *brain injury* with

loss of consciousness at the age of 11 and alcohol abuse for about 5 years. No special medication for treatment of alcohol abuse was prescribed during that time. The patient reported symptoms of anxiety, delusional beliefs, cognitive deficit that he has suffered over the years. He describes affective disorders which were presented with auditory hallucinations and persecutory delusions and rare short periods of elevated mood. His first admission to the inpatient ward in Mental Health Research Center (MHRC) was in May 2014 with a number of psychotic symptoms including delusional beliefs, some somatic symptoms. He was prescribed pharmacological treatment. Over this course, he also participated in group sessions and started with individual therapy. PKG86 continued his treatment in an outpatient department afterwards.

In the summer of 2015 a relapse took place and he was voluntary admitted to MHRC in September, 2015 for two months. He was diagnosed as having schizoaffective disorder complicated by alcoholism. In spite of alcohol abuse the patient had a normal liver and kidney functions. This episode of severe disease presented with suicidal ideation, motor retardation, difficulties to concentrate, insomnia, morning apathy and evening anxiety, low self-esteem, lack of insight, episodes of alcohol abuse. Nevertheless, during his stay in the ward he complied with the regimen, was formally friendly with staff and patients, not initiative though. He was maintained on 150mg of clozapine (CLO) and 900mg of quetiapine (QUE) once daily with a minimal effect in four weeks. He continuously reported anxiety, feeling of guilt for his current state and thoughts that "life is not worth living". TDM of AP and clozapine active metabolite norclozapine (NOR) was conducted. The steady state plasma concentrations of QUE, CLO and NOR were 2207, 964 and 49ng/mL, respectively; (metabolic CLO ratio: metabolite/parent=0.05). The current therapeutic ranges for QUE and CLO are 10 to 600ng/mL, and 350 to 600ng/mL, respectively. The measured concentration of QUE exceeded the upper margin of its therapeutic range in 3times (a laboratory alert). A consultant decision was made to switch PKG86 from QUE to oral aripiprazole (ARI). Then he was maintained on 100mg of CLO, and 20mg of ARI once daily. There

was an improvement in patient's condition within the next two weeks which included normalization of sleep, reduction of anxiety and mood stabilization. In a week after switching, TDM of AP including ARI active metabolite dehydroaripiprazole (DHA) was conducted again. The TDM revealed such results as: the concentrations of CLO and NOR were 770 and 76ng/mL, respectively (metabolic ratio slightly enhanced to 0.10); the concentrations of ARI and DHA were 403 and 45ng/mL, respectively (metabolic ratio: 0.11). The therapeutic range for ARI including DHA is 100 to 500ng/mL. Thus, in contrast to QUE total concentration of active moiety (ARI+DHA) had appropriate value.

The unusual results obtained by TDM had stipulated to determinate pharmacogenetic profile the patient. Patients were genotyped for Cyp1A2, CYP2D6 and CYP2C19 alleles (Table 1).

**Table 1** Genes tested by the assay

Gene	cyp1a2*1f	cyp2d6*3	cyp2d6*4	cyp2c19*2	cyp2c19*3	cyp2c19*17
Genotype	C/C	A/A	G/A	A/A	G/G	T/C

## Discussion

There are many evidences pointing to the fact that measuring of concentration both AP and their active metabolite has a great importance. DHA is the main metabolite of ARI and was reported that it possesses the anti-psychotic activity to that of ARI.<sup>5</sup> At steady state, about 30% of the serum ARI concentration is represented by the major active metabolite DHA. TDM of the sum of ARI+DHA concentrations has a preferred value in the clinical practice, than ARI alone. The optimal ratio of CLO to NOR has not yet been defined, but a ratio of two or more implies that saturation of clozapine metabolism has been reached.<sup>6</sup> It seems that a increase of the CLO/NOR ratio (detected too in PKG86) has potential benefits including both a reduction of such side effects as sedation, weight] gain, metabolic disturbances, and neutropenia, and an increase in efficacy.<sup>7</sup> The above case is reported not only for the unusual PGx but also because it accompanied drug-drug interactions. CLO and QUE co-administration would increase quetiapine level<sup>8</sup> and should be avoided especially for PKG86. Despite the current gap between research studies and the practical tools available to the clinician, it is hoped that in the foreseeable future, PGx will become a critical aid to guide the development of personalized therapeutic regimes with fewer adverse effects. In addition to our opinion, TDM and PGx don't deny one another, but on the contrary they potentiate each other.

## Author's contributions

IIM, NVB, SAI and KVG analyzed the data. IIM, SAI, KVG and NVB conceived and designed the study and supervised the work. IIM, NVB, SAI and KVG wrote the reply to reviewers and the revised manuscript. BAA observed the patient. SAI and PIV performed genotyping of CYP2D6, CYP1A2 and CYP2C19. IIM and NVB performed TDM. IIM, BAA and PIV performed translation. All authors read and approved the final manuscript.

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None.

This approach is effective in detecting abnormal genotypes belonging PKG86 caused by mutations:

Cyp1a2\*1F (163C>A) rs762551;

Cyp2d6\*4 (1846G>A) rs3892097;

Cyp2c19\*17 (-806C>T) rs12248560.

Genotyping revealed an aberrant CYP2D6 genotype (\*4/\*4), explaining why this patient was not able to metabolize ARI at a normal rate. Cyp1a2\*1F is very polymorphic gene. People with the A/A genotype associated with enhanced Cyp1a2 activity are considered as extensive CLO metabolizers, and people with the A/C genotype AC and, especially C/C - poor CLO metabolizers. Such, the high values of CLO concentration could be explained by the patient's PGx.

## Conflict of interest

Author declares that there is no conflict of interest.

## References

- Gervasini G, Benítez J, Carrillo JA. Pharmacogenetic testing and therapeutic drug monitoring are complementary tools for optimal individualization of drug therapy. *Eur J Clin Pharmacol*. 2010;66(8):755–774.
- Rison RA. A guide to writing case reports for the Journal of Medical Case Reports and BioMed Central Research Notes. *Journal of medical case reports*. 2013;7(1):239.
- Baimeeva NV, Miroshnichenko II. Analytical Methods for the Determination of Atypical Neuroleptics (Review). *Pharmaceutical Chemistry Journal*. 2016;50(5):339–345.
- Ivanova SA, Toshchakova VA, Filipenko ML, et al. Cytochrome P450 1A2 co-determines neuroleptic load and may diminish tardive dyskinesia by increased inducibility. *The World Journal of Biological Psychiatry*. 2015;16(3):200–205.
- Lin SK, Chen CK, Liu YL. Aripiprazole and dehydroaripiprazole plasma concentrations and clinical responses in patients with schizophrenia. *J Clin Psychopharmacol*. 2011;31(6):758–762.
- Kang MJ, Song WH, Shim BH, et al. Pharmacologically active metabolites of currently marketed drugs: potential resources for new drug discovery and development. *Yakugaku Zasshi*. 2010;130(10):1325–1337.
- Légaré N, Grégoire CA, De Benedictis L, et al. Increasing the clozapine: norclozapine ratio with co-administration of fluvoxamine to enhance efficacy and minimize side effects of clozapine therapy. *Med Hypotheses*. 2013;80(6):689–691.
- Castberg I, Skogvoll E, Spigset O. Quetiapine and drug interactions: evidence from a routine therapeutic drug monitoring service. *J Clin Psychiatry*. 2007;68(10):1540–1545.