ORIGINAL RESEARCH

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Relationship of the *1846G > A* Polymorphism of the *CYP2D6* Gene to the Equilibrium Concentration Levels of Haloperidol in Patients with Acute Alcoholic Hallucinosis

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ABSTRACT *~ Haloperidol is currently used in addictology for the treatment of acute psychotic disorders, including acute alcoholic hallucinosis. The use of haloperidol is often accompanied by the occurrence of adverse drug reactions (ADRs). There is evidence that CYP2D6 isoenzyme is involved in the biotransformation of haloperidol.* ***Aim:*** *The study aimed to evaluate the relationship of 1846G > A polymorphism of the CYP2D6 gene to the equilibrium concentration levels of haloperidol in patients with acute alcoholic hallucinosis.* ***Material and Methods:*** *The study was conducted on 100 male patients with acute alcoholic hallucinosis (mean age 41.4 ± 14.4 years). The efficacy profile was evaluated using the*

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PANSS (Positive and Negative Syndrome Scale) scale. The safety of therapy was assessed using the UKU Side-Effect Rating Scale and the SAS (Simpson-Angus Scale for Extrapyramidal Symptoms) scale. Genotyping was performed using the real-time polymerase chain reaction (Real-time PCR). Equilibrium plasma concentration levels of haloperidol were investigated using the high-performance liquid chromatography with mass spectrometry (HPLC with MS/MS). ***Results:*** *No statistically significant results were obtained during the therapy efficacy assessment (dynamics of the PANSS score:* GG *genotype (−13.00 [−16.00; −16.00; −11.00]),* GA *genotype (−15.00 [−16.75; −13.00], p = 0.728). There was a statistically significant difference in safety assessment scores (dynamics of the UKU score:* GG *genotype (8.00 [7.00; 10.00]),* GA *genotype (15.00 [9.25; 18.00], p < 0.001); dynamics of the SAS score:* GG *genotype (11.00 [9.00; 14.00]),* GA *genotype (14.50 [12.00; 18.00], p < 0.001). The pharmacokinetic study results showed a statistically significant difference:* GG *(3.13 [2.32; 3.95]),* GA *(3.89 [2.92; 5.26], p = 0.010). Thus, a study conducted on a group of 100 patients with acute alcoholic hallucinosis demonstrated an association between the* 1846G > A *polymorphism of the* CYP2D6 *gene* (rs3892097) *and the safety profile of haloperidol therapy. We also revealed the presence of statistically significant difference in the equilibrium concentration levels of haloperidol in patients with the* GG *and* AG *genotypes.* ***Conclusion:*** *It can be concluded that patients with the* GA *genotype have a higher risk of ADRs compared to patients carrying the* GG *genotype. It is shown that* 1846G > A *polymorphism of the* CYP2D6 *gene* (rs3892097) *has a statistically significant effect on the equilibrium concentration levels of haloperidol.* Psychopharmacology Bulletin. *2023;53(4):15–22.*

Introduction

Alcoholic hallucinosis is a mental disorder characterized by the acute onset, with predominating auditory hallucinations.[1] The incidence of this disorder ranges from 0.4% to 12%.[2] Alcoholic hallucinosis is treated in hospitals, typically with antipsychotic drugs. Haloperidol at a dose of 5–10 mg per day is usually prescribed.[3] When using haloperidol, adverse drug reactions such as akathisia and dystonia often occur.[4]

Studies revealed that haloperidol metabolism occurs with the participation of cytochrome P450 (CYP) 2D6 isoenzyme.[5] Polymorphism of the *CYP2D6* gene (*CYP2D6*4*, *CYP2D6 1846G > T*, *rs3892097*) is the most studied genetic polymorphism leading to deactivation of CYP2D6 isoenzyme and the reduced metabolism of the substrate drugs.[6]

Studies conducted on patients with alcohol use disorders have shown a statistically significant correlation between the *CYP2D6* genetic polymorphism, isoenzyme activity and the efficacy and safety rates of haloperidol.[7,8]

Studies conducted on patients with alcohol use disorders who received haloperidol in injections demonstrated a relationship between the *1846G > A* polymorphism of the *CYP2D6* gene (*rs3892097*) and haloperidol equilibrium concentration levels in plasma ($p = 0.037$).[9]

The aim of this study was to evaluate the relationship of the *1846G > A* polymorphism of the *CYP2D6* gene to the equilibrium concentration levels of haloperidol in patients with acute alcoholic hallucinosis.

Material and Methods

The study enrolled 100 male patients (average age—41.4 ± 14.4 years) with acute alcoholic hallucinosis (alcohol-induced psychotic disorder with hallucinations (F10.52), according to ICD-10) who underwent inpatient treatment at Moscow Research and practical center on Addictions. Haloperidol in injections at a dose of 5–10 mg/day was administered to this cohort of patients for the treatment of acute hallucinatory symptoms. Haloperidol therapy was initiated from the moment of the patient's admission to the emergency department and lasted for 5 days. Along with haloperidol, all patients received minimal standard therapy for 5 days, which included infusions, ion-containing solutions, and vitamins.

The inclusion criteria were the signed informed consent to participate in the study; the diagnosis of alcohol-induced psychotic disorder with hallucinations (F10.52, according to ICD-10); 5 days of haloperidol treatment.

The exclusion criteria were creatinine clearance values < 50 mL/min, creatinine plasma concentration > 1.5 mg/dL (133 mmol/L), body weight less than 60 kg or greater than 100 kg, age ⩾ 75 years, presence of any other psychotropic medications in the treatment regimen other than haloperidol, presence of chronic psychotic disorders, and presence of any contraindications for haloperidol use.

Each patient signed an informed consent for voluntary participation in the study (Protocol No. 14 of October 27, 2020), which was approved by the local ethical committee of the Russian Medical Academy of Continuing Professional Education of the Ministry of Health of Russia.

For genotyping, venous blood samples were collected on the day 6 of haloperidol therapy using the VACUETTE® vacuum tubes (GreinerBio-One, Austria). The *1846G > A* polymorphism of the *CYP2D6* gene (*rs3892097*) was analyzed by real-time PCR using "Dtlite" DNA amplifiers (DNA Technology, Moscow, Russia) on a CFX96 Touch Real-Time System with CFX Manager software (Bio-Rad Laboratories Inc., Hercules, CA, USA) and the "SNP-screen" sets (Syntol, Moscow, Russia). In every set, two allele-specific hybridizations

were used, which allowed simultaneous determination of both alleles of the respective SNP using two fluorescence channels.

Therapeutic drug monitoring of haloperidol was performed by evaluating the equilibrium plasma concentration levels of haloperidol using the high-performance liquid chromatography with mass spectrometry (HPLC with MS/MS). Calibration and control samples were prepared from working standard solutions by dissolving an accurate suspension of the standard sample in methanol followed by dilution to obtain the desired concentrations. To construct the calibration curve, calibration samples were prepared with haloperidol concentrations of 5, 10, 20, 50, 100, 200, 500, 1000, 2000 ng/mL, and control samples with diazepam concentrations of 5 (lower limit of quantification, LLOQ), 15 (low QC), 1000 (medium QC), 1500 ng/mL (high QC). Droperidol at a concentration of 250 ng/mL in acetonitrile was used as an internal standard (IS).

The efficacy of haloperidol therapy was assessed using the PANSS positive subscale.[10] The safety profile of haloperidol therapy was assessed using the UKU Side Effect Rating Scale.[11] and the Simpson-Angus Extrapyramidal Side Effects Scale (SAS).[12] Scale scoring and biomaterial collection were performed on days 1 and 6 of haloperidol treatment.

Statistical analysis was performed in StatsoftStatistica v. 10.0 (Dell Statistica, Tulsa, OK, USA). Statistical analysis of the study results was performed using the methods of nonparametric statistics due to the absence of normal distribution of data, which was checked using the Shapiro-Wilk W-test. The Mann-Whitney U-test was used to compare two samples of continuous independent data, and the Wilcoxon test was used to compare two samples of dependent data. In the case of multiple comparisons, we calculated the adjusted p-values using the Benjamini-Hochberg procedure. Research data are presented in the form of the median and interquartile range (Me [Q1; Q3]).

Results

CYP2D6 genotyping by the polymorphic marker *1846G > A* (*rs3892097)* performed in 100 male patients with acute alcoholic hallucinosis revealed the following data:

1) The number of patients who were homozygous carriers (genotype *GG*) of the *1846G > A* polymorphism of the *CYP2D6* gene was 70 (70%).
2) The number of patients who were heterozygous carriers (genotype *GA*) of the *1846G > A* polymorphism of the *CYP2D6* gene was 30 (30%).

The results of data analysis performed for psychometric assessments (PANSS) and side-effect rating scales (UKU and SAS) on days 1 and 6 in patients who received haloperidol are presented in Table 1.

Then we compared the dynamics of changes in the PANSS positive subscale scores in patients with the *GG* and *GA* genotypes. Statistical analysis of the data on the clinical efficacy profile of haloperidol in patients with different genotypes showed no statistically significant differences: *GG* (−13.00 [−16.00; −11.00]), *GA* (−15.00 [−16.75; −13.00]), p = 0.078.

Table 2 presents the dynamics of changes in the SAS and UKU scores in patients with different genotypes. Statistical analysis of the data on the safety profile of haloperidol in patients with different genotypes by the *1846G > A* polymorphic marker of the *CYP2D6* gene showed statistically significant differences.

Table 3 presents the results of pharmacokinetic study in patients carrying the *GG* and *GA* genotypes.

The *1846G > A* polymorphism of the *CYP2D6* gene (*rs3892097*) was shown to have a statistically significant effect on the equilibrium concentration levels of haloperidol when administered to patients with acute alcoholic hallucinosis (Figure 1).

TABLE 1

Data from the Psychometric Assessments and Side-Effect Rating Scales in Patients Who Received Haloperidol, on Days 1 and 6 of the Study

SCALE	*GG* (N = 70)	*GA* (N = 30)	P*
Day 1			
PANSS	14.50 [13.00; 18.00]	16.00 [15.00; 18.00]	> 0.999
SAS	0 [0; 0]	0 [0; 0]	> 0.999
UKU	0 [0; 0]	0 [0; 0]	> 0.999
Day 6			
PANSS	1.00 [1.00; 2.00]	2.00 [1.00; 2.75]	0.006
SAS	11.00 [9.00; 14.00]	14.50 [12.00; 18.00]	< 0.001
UKU	8.00 [7.00; 10.00]	15.00 [9.25; 18.00]	< 0.001

Note: p* – p-value obtained in Benjamini-Hochberg multiple testing correction (based on the results of Mann-Whitney U test).

TABLE 2

Dynamics of Changes in the SAS and UKU Scores from Days 1 to 6 in Patients with Different Genotypes by the *1846G > A* Polymorphic Marker of the *CYP2D6* Gene

SCALE	*GG*	*GA*	P
SAS	11.00 [9.00; 14.00]	14.50 [12.00; 18.00]	p < 0.001
UKU	8.00 [7.00; 10.00]	8.00 [7.00; 10.00]	p < 0.001

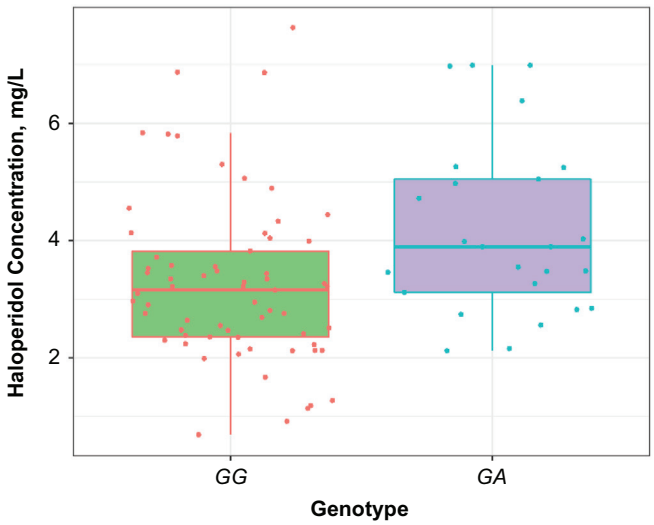
TABLE 3

Equilibrium Concentration Levels of Haloperidol in Patients with Different Genotypes by the *1846G > A* Polymorphic Marker of the *CYP2D6* Gene

GG	*GA*	P
3.13 [2.32; 3.95]	3.89 [2.92; 5.26]	0.010

FIGURE 1

Effect of the *1846G > A* Polymorphism of the *CYP2D6* Gene *(RS3892097)* on the Equilibrium Concentration Levels of Haloperidol



Discussion

Thus, the results of the study showed no statistically significant differences in the efficacy rates of haloperidol therapy in patients with acute alcoholic hallucinosis carrying different genotypes by the polymorphic marker *1846G > A* of the *CYP2D6* gene. Meanwhile, a statistically significant difference in the safety parameters assessed by the UKU and SAS scales was revealed. The dynamics of changes was more pronounced in the group of patients with the *GA* genotype compared to those who were carriers of the *GG* genotype. The equilibrium concentration levels of haloperidol showed a statistically significant difference between the carriers of the *GG* and *GA* genotypes, which confirms the influence of the *CYP2D6* genetic polymorphism on haloperidol concentrations in patients with acute alcoholic hallucinosis.

The results of our study coincide with the results of a study demonstrating an increased incidence of ADRs in patients with alcohol addction treated with haloperidol.[9] Also, there is evidence from a study that the *CYP2D6* genetic polymorphism (*1846G > A*) may affect the concentration levels of haloperidol in patients with alcohol use disorders.[9]

Patients with the *GA* genotype should have the starting dose of haloperidol reduced by 25%, and homozygous *GG* carriers are recommended to be prescribed haloperidol at the standard therapeutic dose. According to the DPWG guidelines, a 50% reduction in the starting dose of haloperidol is recommended for mutant homozygotes.[13] According to our study, a worsening of the safety profile was observed in heterozygous carriers; therefore, it is necessary to adjust the starting dose of haloperidol for this group.

Conclusion

Thus, an association between the *1846G > A* polymorphism of the *CYP2D6* gene (*rs3892097*) and the safety profile of haloperidol was demonstrated in a study conducted on 100 patients with acute alcoholic hallucinosis. A statistically significant difference in the equilibrium concentration levels of haloperidol was found between the carriers of the *GG* and *GA* genotypes, confirming the influence of the *CYP2D6* genetic polymorphism on haloperidol concentration levels in patients with acute alcoholic hallucinosis. ✤

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References

1. Perme B, Vijaysagar KJ, Chandrasekharan R. Follow-up study of alcoholic hallucinosis. *Indian J Psychiatry*. 2003;45:244–246.
2. Jordaan GP, Emsley R. Alcohol-induced psychotic disorder: A review. *Metab Brain Dis*. 2014;29(2): 231–243. doi:10.1007/s11011-013-9457-4.
3. de Millas W, Haasen C. Treatment of alcohol hallucinosis with risperidone. *Am J Addict*. 2007;16(3): 249–250. doi:10.1080/10550490701375269.
4. Ohno Y, Kunisawa N, Shimizu S. Antipsychotic treatment of behavioral and psychological symptoms of dementia (BPSD): Management of extrapyramidal side effects. *Front Pharmacol*. 2019;10:1045. doi:10.3389/fphar.2019.01045.
5. Kozyra M, Ingelman-Sundberg M, Lauschke VM. Rare genetic variants in cellular transporters, metabolic enzymes, and nuclear receptors can be important determinants of interindividual differences in drug response. *Genet Med*. 2017;19(1):20–29. doi:10.1038/gim.2016.33. Epub 2016 Apr 21. PMID: 27101133.

6. Zanger U, Raimundo S, Eichelbaum M. Cytochrome P450 2D6: Overview and update onpharmacology, genetics, biochemistry. Naunyn Schmiedebergs Arch. *Pharmacol*. 2004;369(1):23–37. doi:10.1007/s00210-003-0832-2.
7. Sychev DA, Zastrozhin MS, Smirnov VV, Savchenko LM, Bryun EA, Guschina YuSh, et al. Association of isoenzyme CYP2D6 activity with efficacy and safety profile of haloperidol in patients with compulsive affection for alcohol. *Bulletin of RSMU*. 2015;4:36–39.
8. Sychev DA, Zastrozhin MS, Smirnov VV, Grishina EA, Savchenko LM, Bryun EA. The correlation between CYP2D6 isoenzyme activity and haloperidol efficacy and safety profile in patients with alcohol addiction during the exacerbation of the addiction. *Pharmacogenomics Pers Med.* 2016;9:1–7.
9. Sychev DA, Zastrozhin MS, Miroshnichenko II, Baymeeva NV, Smirnov VV, Grishina EA, Ryzhikova KA, Mirzaev KB, Markov DD, Skryabin VY, Snalina NE, Nosikova PG, Savchenko LM, Bryun EA. Genotyping and phenotyping of CYP2D6 and CYP3A isoenzymes in patients with alcohol use disorder: Correlation with haloperidol plasma concentration. *Drug MetabPersTher*. 2017;32(3):129–136. doi:10.1515/dmpt-2017-0021. PMID: 28787271.
10. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13(2):261–276. doi:10.1093/schbul/13.2.261.
11. Lingjaerde O, Ahlfors UG, Bech P, et al. The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. *Acta Psychiatr Scand Suppl*. 1987;334:1–100. doi:10.1111/j.1600-0447.1987.tb10566.
12. Simpson GM, Angus JWS, A rating scale for extrapyramidal side effects. *Acta PsychiatrScand*. 1970;212:11–19. doi:10.1111/j.1600-0447.1970.tb02066.x.
13. PharmGKB. URL:https://www.pharmgkb.org/guidelineAnnotation/PA166104988. (Accessed 11.10.2021).