

Factors affecting the development of adverse drug reactions to β -blockers in hospitalized cardiac patient population

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Abstract: The aim of the present study was to undertake a study on the prevalence of cytochrome P450 2D6 (CYP2D6) poor metabolizer alleles (*3, *4, *5, and *6) on a Montenegrin population and its impact on developing adverse drug reactions (ADRs) of β -blockers in a hospitalized cardiac patient population. A prospective study was conducted in the Cardiology Center of the Clinical Center of Montenegro and included 138 patients who had received any β -blocker in their therapy. ADRs were collected using a specially designed questionnaire, based on the symptom list and any signs that could point to eventual ADRs. Data from patients' medical charts, laboratory tests, and other available parameters were observed and combined with the data from the questionnaire. ADRs to β -blockers were observed in 15 (10.9%) patients. There was a statistically significant difference in the frequency of ADRs in relation to genetically determined enzymatic activity ($P < 0.001$), with ADRs' occurrence significantly correlating with slower CYP2D6 metabolism. Our study showed that the adverse reactions to β -blockers could be predicted by the length of hospitalization, CYP2D6 poor metabolizer phenotype, and the concomitant use of other CYP2D6-metabolizing drugs. Therefore, in hospitalized patients with polypharmacy CYP2D6 genotyping might be useful in detecting those at risk of ADRs.

Keywords: adverse drug reactions, β -blockers, CYP2D6, pharmacogenetics

Introduction

According to the latest definition, formulated in 2010, adverse effect is a harmful and unintentionally caused reaction to a medicine.¹ Adverse drug reactions (ADRs) are a common cause of morbidity and mortality, with contribution of numerous risks factors. It is estimated that ADRs could be prevented in ~50% of cases.²⁻⁵

Of all cardiovascular drugs, most adverse effects are caused by β -blockers, angiotensin converting enzyme inhibitors, and calcium channel blockers.^{6,7}

β -Blockers are recommended as a first-line agent for various diseases, including heart failure, hypertension, and angina, as well as after myocardial infarction.^{8,9} However, β -blocker therapy often produces variable responses among patients.^{10,11} Individual response to β -blockers in other clinical settings is substantially influenced by genetic variation in adrenergic signaling¹² and drug metabolism pathways, most notably in the cytochrome P450 2D6 (CYP2D6) enzyme.¹³⁻¹⁵

CYP2D6 is one of the most important metabolic enzymes, responsible for the biotransformation of 25% of all drugs, including most β -blockers.^{16,17} The observed interindividual variation in CYP2D6 enzyme activity is mainly due to its genetic polymorphism, which significantly affects the metabolism of ~50% of its substrate drugs.¹⁸

More than 150 alleles lead to four distinct phenotypes of drug metabolism,¹⁹ described as ultrarapid metabolizer, extensive metabolizer (EM), intermediate metabolizer, and poor metabolizer (PM). However, ~98% of the PM phenotype can be explained by three single-nucleotide polymorphisms (SNPs), ie, rs35742686 (2549delA), rs3892097 (1846G>A), and rs5030655 (1707delT) corresponding to alleles *3, *4, and *6, respectively, or a complete deletion of *CYP2D6* (*5).^{20–22} In addition to the loss of function, *CYP2D6* enzyme activity could be significantly decreased due to gene polymorphism, and the SNPs leading to this effect include rs1065852 (100C>T, *CYP2D6**10)²³ present in 20% of the European population.²⁴

The aim of the present study was to examine the frequency of *CYP2D6* PM alleles (*3, *4, *5, *6, and *10) in a Montenegrin population, and to determine its impact on developing ADRs of β -blockers in a hospitalized cardiac patient population.

Methods

A prospective study was conducted in the Cardiology Center of the Clinical Center of Montenegro and included 138 patients who had received any β -blocker in their therapy.

Before enlisting in the study, patients were given all necessary information about the study design, after which they signed an informed consent. The ethics committee of the Clinical Center of Montenegro approved the implementation of the research, which was conducted in accordance with the Declaration of Helsinki.

The exclusion criteria were as follows: age younger than 18 years and older than 80 years, dementia or other causes of disorientation, severe illness (eg, cardiogenic shock, pulmonary edema, etc), hematological disorders, significant renal and liver failure, short period of hospitalization (<3 days), and patient's refusal to participate in the trial. In addition, coadministration with major *CYP2D6* inhibitors was contraindicated (ie, fluoxetine, levomepromazine, lobelin, methadone, paroxetine, quinidine, and trifluoperidol).¹⁸

We defined ADRs according to the definition of the World Health Organization (WHO),¹ and for each adverse reaction determined the causal relationship with the drug according to the Naranjo algorithm.²⁵ Also, we determined the severity of the ADRs according to the criteria of the WHO, as well as the type (A: based on the drug's pharmacologic properties; B: idiosyncratic, unexpected; C: chronic effects related to long-term drug use), according to the classification proposed by Edwards and Aronson.²⁶

For the study, a special questionnaire was designed (Figure S1). It consisted of questions about the medication that the patient received during hospitalization in the Center of Cardiology.

The interview was conducted in three steps. First, the patients were asked the standard open question: "Have you noticed or felt any adverse reaction of the drug?" If the answer was yes, the ADRs were recorded. Then the patients were asked about complaints to the various organ systems: these questions helped the patients to "remember" the ADRs. Finally, the patients were asked for adverse reactions mentioned in the "Summary of Product Characteristics", in relation to drugs administered during hospitalization. Data from the patients' medical charts, laboratory tests, and other available parameters were observed and combined with the data from the questionnaire.

All patients who received β -blockers were *CYP2D6* genotyped. On the basis of available literature^{27,28} and *CYP2D6* allele nomenclature,²⁹ for the purpose of the study, five variants were identified and included in the analysis. These variants are considered to be the most common genetic determinants of *CYP2D6* PM phenotypes: *CYP2D6**3 (2549delA, rs35742686), *CYP2D6**4 (1846G>A, rs3892097), *CYP2D6**5 (gene deletion), *CYP2D6**6 (1707delT, rs5030655), and *CYP2D6**10 (100C>T, rs1065852).

DNA was extracted from whole-blood samples using the PureLink[®] genomic DNA kit (Thermo Fisher Scientific, Waltham, MA, USA). Genotyping for *CYP2D6**3, *4, and *6 was carried out using the real-time PCR method on a Mastercycler[®] ep realplex² (Eppendorf AG, Hamburg, Germany), with the use of TaqMan Genotyping Master Mix 2X (Thermo Fisher Scientific) and the corresponding TaqMan DME genotyping Assays (Thermo Fisher Scientific). Genotyping for *CYP2D6**5 and *10 was conducted according to the previously described long-PCR tetra-primer^{30,31} and allele-specific PCR³² methods, with minor modifications. Analyses were performed at the Faculty of Medical Sciences, University of Kragujevac.

Statistical data analysis was performed using IBM SPSS Statistics 22 (IBM Corporation, Armonk, NY, USA). Results are presented as frequency, percent, and mean $\pm$ standard deviation. For parametric data, independent sample *t*-test was used to test differences between groups. The Mann–Whitney *U*-test was used for obtaining the significance between ordinal data. The chi-squared test or Fisher's exact test was used to test the differences between nominal data (frequencies), including Hardy–Weinberg equilibrium.

The association between potential risk factors and ADRs was evaluated using binary logistic regression, expressing the strength of association by crude and adjusted odds ratio with 95% confidence intervals. A P -value of <0.05 was considered significant.

Results

One hundred and thirty-eight patients on β -blocker therapy were included in the study. Of those, 66 (47.8%) patients were treated with metoprolol (dose 25–100 mg), 36 (26.1%) with carvedilol (dose 6.25–50 mg), 33 (23.9%) with bisoprolol (dose 2.5–10 mg), and three (2.2%) with nebivolol (dose 5 mg). The basic characteristics of the patients and the frequencies of *CYP2D6* variants, alleles, and genotypes are given in Tables 1 and 2, respectively.

ADRs to β -blockers were observed in 15 (10.9%) patients. Most ADRs were related to the use of carvedilol and metoprolol (six patients, ie, 8.0% each), followed by bisoprolol (three patients, ie, 4.0%). The most common ADRs were bradycardia (44.4%), dizziness (22.2%), headache (11.1%), hypotension (5.5%), cold lower extremities (5.5%), pain in the extremities (5.5%), and nightmares (5.5%). The characteristics of ADRs to β -blockers and the levels of intervention are given in Table 3.

Genotyping of patients receiving β -blockers showed that more than half belonged to the group of EMs (54.3%). The frequency of PMs was 37.6%, 5.1% of respondents had no enzymatic activity, while 1.4% of patients had intermediate and very PM phenotypes. There was a statistically significant difference in the frequency of ADRs in relation to genetically determined enzymatic activity ($P<0.001$), with the

Table 1 Baseline data of the patients

Characteristic	Patients on β -blocker therapy (n=138)
Age (years), mean $\pm$ SD	59.5 $\pm$ 9.8
Males, n (%)	98 (71)
Body mass index (kg/m ²), mean $\pm$ SD	28.2 $\pm$ 3.8
Active smokers, n (%)	55 (39.9)
Arterial hypertension, n (%)	106 (76.8)
Diabetes mellitus, n (%)	32 (23.2)
Hypercholesterolemia, n (%)	63 (45.7)
Family history of CAD, n (%)	49 (35.5)
Obesity, n (%)	34 (24.6)
Number of drugs, median (range)	8 (2–16)
Duration of hospitalization (days), median (range)	6 (1–29)
ADRs, n (%)	15 (10.9)

Abbreviations: SD, standard deviation; CAD, coronary artery disease; ADR, adverse drug reaction.

Table 2 Frequencies of *CYP2D6* gene variations, alleles, and genotypes in Montenegrin patients on β -blocker therapy

Population genetics parameters	Observed frequency	95% confidence interval
Gene variation		
2549delA	0.033 (9/276)	0.017–0.062
1846G>A	0.181 (50/276)	0.140–0.231
Gene deletion	0.014 (4/276)	0.004–0.038
1707delT	0.025 (7/276)	0.011–0.053
100C>T	0.130 (36/276)	0.096–0.176
Allele		
<i>CYP2D6</i> *1	0.739 (204/276)	0.684–0.787
<i>CYP2D6</i> *3	0.029 (8/276)	0.014–0.057
<i>CYP2D6</i> *4	0.178 (49/276)	0.137–0.227
<i>CYP2D6</i> *5	0.014 (4/276)	0.004–0.038
<i>CYP2D6</i> *6	0.025 (7/276)	0.011–0.053
<i>CYP2D6</i> *10	0.014 (4/276)	0.004–0.038
Genotype		
Extensive metabolizer		
<i>CYP2D6</i> *1/*1	0.543 (10/138)	0.460–0.624
Intermediate metabolizer		
<i>CYP2D6</i> *1/*10	0.014 (2/138)	0.001–0.055
Poor metabolizer		
<i>CYP2D6</i> *1/*3	0.051 (7/138)	0.023–0.103
<i>CYP2D6</i> *1/*4	0.275 (38/138)	0.208–0.355
<i>CYP2D6</i> *1/*5	0.014 (2/138)	0.001–0.055
<i>CYP2D6</i> *1/*6	0.036 (5/138)	0.014–0.085
Very poor metabolizer		
<i>CYP2D6</i> *4/*10	0.014 (2/138)	0.001–0.055
No enzyme activity		
<i>CYP2D6</i> *3/*5	0.007 (1/138)	0.000–0.045
<i>CYP2D6</i> *4/*4	0.022 (3/138)	0.005–0.065
<i>CYP2D6</i> *4/*5	0.007 (1/138)	0.000–0.045
<i>CYP2D6</i> *4/*6	0.014 (2/138)	0.001–0.055

Table 3 Characteristics of detected ADRs

Characteristic	ADRs in patients on β -blocker therapy (n=15) (%)
Type	
Type A	15 (100)
Type B	0 (0)
Type C	0 (0)
Causality	
Certain	0 (0)
Probable	3 (20)
Possible	12 (80)
Level of intervention	
Level 1 (no change in dose)	3 (20)
Level 2 (dose changed or drug stopped)	10 (66.66)
Level 3 (drug stopped + additional therapy)	2 (13.33)
Level 4 (transfer to intensive care unit)	0 (0)
Severity	
Serious ADRs	4 (26.66)
Nonserious ADRs	11 (73.33)
Outcome	
Recovery without consequences	15 (100)
Recovery with consequences	0 (0)

Abbreviation: ADR, adverse drug reaction.

occurrence of ADRs significantly correlating with slower CYP2D6 metabolism (Figure 1).

The influence of different predictors on the outcome of interest (ie, ADRs to β -blockers) was analyzed in two steps. First, a univariate logistic regression model was used to assess the influence of single predictors, and a subsequent multivariate model analyzed the simultaneous influence of all predictors confirmed as significant in the single predictor analysis.

In the univariate logistic regression model, statistically significant predictors of ADRs to β -blockers were the number of days of hospitalization ($P=0.019$), enzyme activity (PMs [$P=0.016$], and very PM and metabolizer without enzyme activity [$P<0.001$] compared to EM and intermediate metabolizer as the reference category) and the concomitant use of other drugs that are metabolized by the same CYP enzyme system ($P=0.001$).

The multivariate logistic regression model included a statistically significant predictor from the univariate logistic regression model. As regards the CYP2D6 enzyme activity in the sample analyzed, it was necessary to compress a small number of variables into fewer categories: 1) EM and intermediate metabolizer and 2) PMs, very PMs, and metabolizers without enzyme activity. The multivariate logistic regression model was statistically significant ($P<0.001$), without significant multicollinearity between predictors. The interaction of predictors in the model was not statistically significant. In other words, the predictors were orthogonal (ie, they were not collinear), and the statistical interference on the model was reliable.

In the multivariate logistic regression model, statistically significant predictors of ADRs to β -blockers were longer hospitalization ($P=0.008$), slower enzymatic activity

Table 4 Multivariate logistic regression with ADRs on β -blockers as the dependent variable

Independent variable	Multivariate logistic regression	
	OR (95% CI)	P-value
Number of days of hospitalization	1.13 (1.03–1.24)	0.008
Enzyme activity (two categories)	34.60 (4.80–49.31)	<0.001
Concomitant use of other drugs that are metabolized by the same CYP enzyme system	25.44 (5.01–29.29)	<0.001

Abbreviations: ADR, adverse drug reaction; OR, odds ratio; CI, confidence interval; CYP, cytochrome P450.

($P<0.001$), and concomitant use of other drugs that are metabolized by CYP2D6 ($P<0.001$) (Table 4).

Discussion

β -Blockers are an important class of cardiovascular drugs used in hypertension, heart failure, and acute myocardial infarction, which represent one of four leading agents that reduce cardiovascular mortality and morbidity. Although >100 β -blockers have been developed, only ~30 are in clinical use.³³

Polypharmacy, a common practice in cardiovascular pharmacotherapy, may give rise to ADRs. The prevalence of cardiovascular drug-induced adverse reactions is 2.4 times higher compared to other drugs.³⁴ Numerous studies have shown that the administration of β -blockers is associated with higher incidences of ADRs compared to other cardiovascular drugs.^{35,36} The present study was conducted in order to analyze ADRs in patients with cardiovascular diseases treated with β -blockers, and to assess the modulating role of CYP2D6 SNPs.

The results of our study showed that ADRs to β -blockers appear in every ninth patient, which is twice compared to the data in the literature.⁶ This may be partly due to the use of different drugs from this class studied or a different study design. The most common ADRs observed in our study population were bradycardia and dizziness, while other adverse effects, such as fatigue, cold hands, headache, stomach upset, constipation, and diarrhea, were rare. These results are in accordance with the data from the literature.^{33–35} As expected, the ADRs observed were mainly type A reactions (based on the drug's pharmacologic properties), which could be explained by the study design, target population, and the well-known β -blocker safety pattern. In particular, the type A reactions are dose-related and more likely to occur in PMs.

It is well known that polymorphism of the CYP2D6 gene plays an important role in the biotransformation of β -blockers.^{22,37} Numerous studies have found the CYP2D6

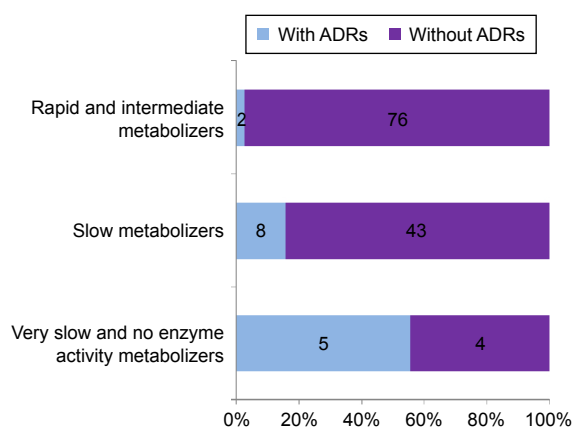


Figure 1 Distribution of ADRs of β -blockers according to CYP2D6 enzyme activity. **Abbreviations:** ADR, adverse drug reaction; CYP2D6, cytochrome P450 2D6.

genotype to be a major determinant of plasma concentration of metoprolol,^{13,38–41} the most frequently prescribed β -blocker.¹³ However, reports on the adverse effects of β -blockers in relation to *CYP2D6* polymorphism are conflicting, as some authors observed that the PM genotype conveys significantly higher risk for the development of ADRs^{12,13,42–44} while others did not detect any significant difference in drug response among the *CYP2D6* genotype groups.^{39,40,45–47} In a retrospective study, Wuttke et al¹² identified 24 patients treated with metoprolol who had experienced pronounced adverse effects. Genotyping revealed a fivefold higher frequency of PM in this group compared to the control population, with the *CYP2D6* PM phenotype exhibiting up to tenfold higher plasma concentrations of metoprolol compared to EMs. Goryachkina et al,¹³ investigating the effect of *CYP2D6* polymorphism in 187 acute myocardial infarction patients on metoprolol treatment, observed the most pronounced bradycardia in genotypically PMs. A similar association was observed in several larger trials, including the MERIT-HF⁴⁴ and the Rotterdam Study,⁴² reporting significantly lower heart rates and blood pressure in carriers of a *CYP2D6**4 defective allele. On the other hand, there have been a number of reports showing no relationship between metoprolol response and the *CYP2D6* genotype,^{39,40,45,47} but the lack of significance was usually due to the small sample size,^{39,40,45,47} lack of genotyping data on all important PM *CYP2D6* SNPs,^{45,47} or the presence of confounding variables that are likely to obscure differences in clinical effects.⁴⁵

In the present study, we examined the frequency and effect of the most important *CYP2D6* PM SNPs in patients treated with β -blockers. The results showed that most of our patients were EMs, while the least frequent were intermediate and very PMs. These data are consistent with those obtained in other white populations.^{48–52} As for the ADRs to β -blockers, they were significantly more common in carriers of the *CYP2D6* genotype, which predicts poor metabolism. This corresponds well with the reports of higher incidence of ADRs in *CYP2D6* PMs,^{10,18,53–55} indicating the importance of *CYP2D6* genotyping in Montenegrin patients on β -blockers. Further studies, including genotyping for duplication of the functional *CYP2D6* gene, might further reveal the possible effect of the ultrarapid metabolizer phenotype on the resistance to β -blockers therapy. In addition to the *CYP2D6* activity, our study showed that ADRs to β -blockers are more likely to occur in patients with comedications and longer hospitalization, which fits into the well-known pattern. Significance in the multivariate regression model used without collinearity

between predictors implies that the risk factors for the ADRs to β -blockers could be reliably identified.

As regards the possible limitations, β -blocker plasma monitoring could significantly improve the reliability of our study, although these drugs do not fulfill the criteria for routine therapeutic drug monitoring.⁵⁶

Conclusion

Our study showed that the adverse reactions to β -blockers could be predicted by the length of hospitalization, genotype-inferred *CYP2D6* PM phenotype, and the concomitant use of other *CYP2D6*-metabolized drugs. Therefore, in hospitalized patients with polypharmacy that includes β -blockers, *CYP2D6* genotyping might be useful in detecting those at risk of ADRs.

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Disclosure

The authors report no conflicts of interest in this study.

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Supplementary material

Patient name: Reason for admission to the hospital:

Age:
.....

Sex: BMI:
.....

Duration of hospitalization:
.....

Date of registration: Allergies:
.....

Drug profile:

Start	Drug name	Dose	Form	Route	Indication	Start	Stop

Have you noticed or felt any adverse reaction of the drug? ☐ Yes ☐ No

If yes, which complaints: Since:

Do you have complaints about:

	Which complaints?	Since?	Drug
Skin, hair, nails			
Muscles			
Joints, bones			
Lice, glava			
Face, head			
Eyes, visibility			
Hearing, odor, taste			
Throat, voice			
Airways			
Heart, blood circulation			
Stomach, digestion			
Kidneys, urinary tract			
Sleeping			
Nerve system			
Mental condition			
Other complaints			

Have you ever experienced the following adverse drug reactions?
.....
.....

Did you have these complaints before you used these medicines? ☐ Yes ☐ No

Can you suggest other possible causes of the complaints?
.....
.....

Figure S1 Questionnaire regarding adverse drug reaction.

Abbreviation: BMI, body mass index.

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