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PHARMACOGENETIC PROFILE AND PERSONALIZATION POSSIBILITIES IN TREATMENT OF PATIENTS WITH CHRONIC PELVIC PAIN SYNDROME

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ABSTRACT — Chronic pelvic pain syndrome (CPPS) is equally common in both men and women, causes worsening quality of life, social isolation and disability. The treatment of CPPS requires long-term pharmacotherapy associated with the development of class-specific side effects of nonsteroidal anti-inflammatory drugs (NSAIDs).
Genetic study of the carriage of polymorphic alleles of the CYP2C9 gene involved in the metabolism of non-steroidal anti-inflammatory drugs (NSAIDs) prescribed to patients with CPPS is an urgent and in-demand task of modern healthcare.
This study allows us not only to determine the genotypes of patients with CPPS but also to identify ways of personalized approach to therapy.

KEYWORDS — chronic pelvic pain syndrome, non-steroidal anti-inflammatory drugs, pharmacogenetics, CYP2C9, personalized algorithms.

INTRODUCTION

Chronic pelvic pain syndrome (CPPS) has a relatively equal prevalence throughout the world. According to the WHO, every fifth person on the planet suffers from chronic pelvic pain caused by diseases of various body organs and systems. More than 60% of women and 70% of men go to specialists because of CPPS. [2].

Nonsteroidal anti-inflammatory drugs (NSAIDs) efficacy in CPPS can be explained by the intracellular enzyme cyclooxygenase (COX) inhibition, which is involved in the synthesis of a variety of prostaglandins and leukotrienes regulating development of the inflammatory response. However, drugs from this group have serious class-specific adverse reactions (ADR) [1, 4].

NSAIDs are metabolized by cytochrome P450 enzymes, among which CYP2C9 plays a major role. The CYP2C9 gene is characterized by significant polymorphism. The most clinically important alleles are CYP2C9*2 and CYP2C9*3, which are associated with a slow rate of metabolic reactions of NSAIDs [8]. These genetic features facilitate the accumulation of drugs, increase the area under the concentration curve and as result lead to ADR. On the other hand, active metabolizers are able to eliminate NSAIDs in a shorter time what may reduce the clinical efficacy of drugs.

Therefore, the aim of this study was to study the frequency of polymorphic alleles of the CYP2C9 gene and to develop approaches for the personalized administration of NSAIDs in patients with CPPS.

MATERIALS AND METHODS

The research was carried out at the Department of Pharmacology and the Department of Nervous Diseases of the Astrakhan State Medical University (Russia). The ethical principles of Helsinki Declaration of the World Medical Association (1964, 2000) were observed in the work with patients. Informed consent was obtained from all patients that participated in our study. The study involved 102 patients with CPPS. They underwent a comprehensive clinical, laboratory and genetic testing based on which events for personalized therapy were developed.

Inclusion criteria were patient's informed consent; established diagnosis of CPPS; adverse drug reaction on NSAIDs in the medical history; the age from 18 to 70 years; for women: absence of pregnancy and contraceptive usage.

Exclusion criteria were: severe concomitant liver and renal diseases; the presence of decompensated concomitant diseases, including cancer, requiring constant intake of drugs from other groups; CHD. Angina pectoris, functional class III-IV; administration of drugs-substrates of CYP2C9, including warfarin; presence of diabetes mellitus and metabolic syndrome; presence of strokes and heart attacks in the anamnesis; hypotrophy, cachexia, severe asthenic syndrome; presence of genetic and mental illnesses; age under 18 and over 70 years; lack of compliance to therapy.

The intensity of pain syndrome and clinical, instrumental, laboratory and pharmacogenetic tests of the CYP2C9 gene were evaluated in all patients of the main observation group (n=102) enabling to develop their personalized therapies.

The polymorphism of CYP2C9 gene was determined by polymerase chain reaction after first DNA isolating from blood samples according to generally accepted methods at the D.O. Ott Research Institute of Obstetrics, Gynecology and Reproductology, St. Petersburg.

The average age of the patients was 49.7±13.43 years. There were 46 men (46%) and 54 women (54%). In accordance with the visual-analog scale (VAS) the pain intensity index was used for a comprehensive evaluation of the pain syndrome

Statistical processing of the results was carried out by the methods of parametric and nonparametric statistics. Correspondence of the genotype frequencies in the populations to the Hardy-Weinberg equilibrium was determined by the χ^2 method. The reliability of group differences for the parameters following the normal distribution was evaluated using the Student's test (T). The differences were considered significant at $p < 0.05$. To study the causal relationship between the phenomena, the regression analysis method was used using the Excel package of additional statistical programs. There was applied regression analysis using Excel package of additional statistic software to study the cause-effect relationship between the events.

RESULTS

In the study of CYP2C9 genotypes equilibrium distribution at the polymorphic markers C43OT and A1075C according to the Hardy-Weinberg proportion it was found that the distribution frequencies of polymorphic genotypes in the total study group (n=100) were equally distributed — χ^2=0,2445; p=0,6210 (p>0.05).

According to the results of conducted genotyping *2/n (rs1799853 CYP2C9*2 (C43OT)) phenotype was found in 10% of cases which according to the consortium's Guidelines (CPIC) for CYP2C9, has an activity index of 1.5 and corresponds to the concept of *intermediate metabolism* — Intermediate metabolizer.

The polymorphic slow allele rs1057910 CYP2C9*3 (A1075C) with an activity index of 0.5 was detected in 22% of cases. Since intermediate metabolizers are phenotypically individuals with reduced CYP2C9 function, it was decided to combine them into one general subgroup — individuals with reduced function. Which in the total sample of the study (n=102) was 32%. In patients with CPPS, 68% were found to be normal metabolizers with the wt/wt genotype.

When comparing patient's complaints, anamnesis of the disease, life history with concomitant pathology, the efficacy and tolerability of NSAIDs in outpatient practice of the anamnesis and finally taking into account the identified genotypes there were identified interesting features which in our opinion require understanding, systematization and further large-scale studies.

There were patients with CPPS who had mainly a long *experience* of the disease — 10 or more years in the group of slow metabolizers. While in the group of normal metabolizers this number was much lower: 57.5% VS 89% (Table 1).

90.6% of slow metabolizers with HTB on admission had a pain intensity value on a visual-analog scale (VAS) of 8 or more points. The pain intensity in the group of normal metabolizers was less marked — 7 points (57.5 %).

According to the materials of medical documentation and medical history of the disease, 46% of patients with CPPS who are normal metabolizers have weak efficacy of NSAIDs taken on an outpatient basis. On the other hand, in the group of patients with slow CYP2C9 allele more patients showed the effectiveness of NSAIDs in anamnesis, however, 31% of them had ADR of the gastrointestinal tract that contributed to the discontinuation or replacement of drugs in this group.

Character of the concomitant pathology depending on the CYP2C9 genotype carrier also requires attention. Among the concomitant pathologies, CVS diseases took first place in the frequency of prevalence (42.9%) in patients with CPP who are normal metabolizers. The second most important were gastrointestinal diseases — 12.5%. Among the cardiovascular pathologies, the leading ones were stage II hypertension (20.4%), secondary hypertension (10%) and CHD. Angina pectoris (functional class II) was observed in 7.5% of patients, atrial fibrillation — in 5%.

In the group of CPPS patients with the slow CYP2C9 allele, gastrointestinal tract pathology was most common, among which erosive and ulcerative lesions were recorded in the history of 24% patients, and the symptoms of the last exacerbation were noted less than 5 months ago. It was found by the method of regression analysis that in slow metabolizers there is a relationship between the intensity of pain in CPPS according to the VAS and the frequency of erosive and ulcerative diseases in the history — determination coefficient R^2=2,22.

It can be assumed that, in addition to the well-known *vicious circles* of the CPPS pathogenesis formation there is a mutual conditioning and aggravating effect of NSAIDs on the gastrointestinal mucosa, on the one hand, and NSAIDs *tolerance* depending on the initial state of the gastrointestinal tract, on the other. Patients with CPPS carrying the slow CYP2C9 allele,

Table 1. *Clinical and pharmacogenetic features of the examined patients with CPPS (n=102)*

№	Clinical and anamnestic parameters.	Normal CYP2C9 wt/wt metabolizers (n=70)	Poor metabolizers rs1057910 CYP2C9*3 (A1075C) rs1799853 CYP2C9*2 (C430T)/(n=32)
1	Duration of the disease		
	More than 10 years	57,5%	84%
	More than 5 years	22,5%	12,5%
	More than 1 year	30,4%	3,5%
2	Assessment of pain intensity (VAS)		
	≥8 points	25%	90,6%*
	7 points	57,5%	9,4%
	≤6 points	17,5%	-
3	Efficacy and tolerability of NSAIDs in medical history		
	NSAIDs in tablet form, taken in outpatient treatment	Low efficiency 46%	Significantly high efficiency
	ADR when taking NSAIDs at any time in the anamnesis (dyspepsia, epigastric pain, heartburn, flatulence)	5,5%	31%
4.	Concomitant pathology		
	Gastrointestinal tract	11%	30%*
	Erosive-peptic ulcer disease of the gastrointestinal tract with an exacerbation less than three months ago	-	24%
	Erosive-peptic ulcer disease of the gastrointestinal tract with exacerbation more than 2 years ago	6,5%	2%*
	Chronic colitis	2,5%	1%
	Chronic gastritis	3%	5%
	CVS	42,9%	12,5%
	Stage II hypertension	20,4%	-
	Secondary arterial hypertension	10%	12,5%
	Coronary artery disease. I functional class angina pectoris II functional class, NC0	7,5%	-
	Atrial fibrillation	5%	-
	Gynecological diseases (fibroids, adnexitis)	5,5%	9,3%
	Prostate adenoma, chronic prostatitis	8,6%	6,2%
	Chronic pyelonephritis	4,5%	-

** — Statistically significant relationship between the studied parameters, determined by the method of regression analysis. Determination coefficient R2>0.8*

when taking NSAIDs, experience gastrointestinal complications, are forced to refuse to take NSAIDs group drugs, which leads to the inflammatory reaction persistence, prolongation of the pathological process and even cause chronicity of pain syndrome.

Cardiovascular system pathology in this group of patients was significantly less frequent than the pathology of the gastrointestinal tract and was diagnosed in 12.5% of patients, mainly in the form of secondary hypertension.

Gynecological diseases in women carrying the slow CYP2C9 allele were registered slightly more often than in the group of conventional metabolizers of 9.3%VS5.5%. Urological symptoms in men of both clinical observation subgroups were recorded with the approximately same frequency of 8.6%VS6.2%.

DISCUSSION

Since NSAIDs are prescribed for long-term treatment of CPPS and the majority of patients are elderly people with unfavorable comorbid diseases, the development of methodological approaches which take into account the risk factors for the ADR development, the presence of concomitant pathology and genetic characteristics of the NSAIDs metabolism is a serious medical and social task.

Therapeutic recommendations for NSAIDs prescribing depending on the carriage of CYP2C9

genotypes were developed for CYP2C9 and NSAIDs at the guidelines of the Clinical Pharmacogenetics Implementation Consortium (CPIC) [3].

These Consortium recommendations for celecoxib, flurbiprofen, lornoxicam, ibuprofen and meloxicam based on the CYP2C9 phenotype provide recommendations for normal (Activity score 2), intermediate (Activity score 1.5; 1.0) and slow metabolizers (Activity score 0.5) for the choice of NSAIDs [3]. These approaches are based on the carriage of the CYP2C9 genotype, pharmacokinetic and pharmacodynamic characteristics of NSAIDs.

The therapeutic recommendations of the Clinical Pharmacogenetics Implementation Consortium (CPIC) for NSAIDs can be applied for both short-term and long-term pharmacotherapy.

These recommendations are most stringent for intermediate (IM) and slow metabolizers (PM) of CYP2C9. Recommendations relate both to the choice of drugs — the possibility of treatment with alternative drugs, most of which are not metabolized by CYP2C9 (for example, naproxen, aceclofenac, sulindac, etc.) and suggestions for the prescribed NSAIDs dose titrating.

Considering the broad therapeutic index of NSAIDs, reducing the dose of drugs for normal metabolizers is not recommended. Meanwhile, for intermediate and slow metabolizers it is recommended to prescribe therapy with the lowest initial dose with next titrating it to the clinical effect. For celecoxib and flurbiprofen, the FDA recommends that in slow CYP2C9 (PM) metabolizers the initial dose should be reduced by 75–50%, followed by titration to clinical effect.

Previous clinical studies have shown the least adverse effects of celecoxib and naproxen on the CVS. [7].

These results are shown in the Russian clinical guidelines for the rational use of NSAIDs. Therefore, when developing events for personalized therapy of CPPS in patients with risk for cardiovascular complications, we recommend to use celecoxib selecting an individual dose based on the CYP2C9 genotype. [5, 6].

With the slow CYP2C9*1/3* and CYP2C9*3/3* genotype carriage the area under the curve AUC of celecoxib and flurbiprofen increases, and the FDA has made warnings in the instructions for these drugs and recommendations for dose reduction [3]. Therefore, in the case of CYP2C9*3 carriage and the risk of gastrointestinal complications, aceclofenac (aertal) may be prescribed, the pharmacokinetics of which are not significantly affected by the genetic variants of CYP2C9 in vivo and /or there is insufficient evidence to make a recommendation to present clinical practice guide (CPIC).

According to the results of our research, it might be concluded that the pharmacogenetic study of CYP2C9 gene polymorphic alleles carriage is an informative, accessible and non-invasive method that helps to determine the pharmacogenetic profile of patients with CPPS and identify ways of pharmacotherapy personalization taking in account a particular comorbid pathology.

REFERENCES

1. **Dilger K., Herrlinger C., Peters J., et al.** Effects of celecoxib and diclofenac on blood pressure, renal function, and vasoactive prostanoids in young and elderly subjects. J Clin Pharmacol. 2002; 42: 985–994. PMID: 12211224
2. **Fall M, Baranowski A, Elneil S et al.** EAU guidelines on chronic pelvic pain. Eur Urol 2010 Jan;57(1):35–48. PMID: 19733958 DOI: 10.1016/j.eururo.2009.08.020
3. **Katherine N. Theken, Craig R. Lee, Li Gong, Craig R. Lee , Kelly E. Caudle et all.** Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) for CYP2C9 and Nonsteroidal Anti-Inflammatory Drugs/CPIC GUIDELINE 19 March 2020. PMID: 32189324 https://doi.org/10.1002/cpt.1830
4. **Solomon D. H., Schneeweiss S., Glynn R. J. et al.** Relationship between Selective Cyclooxygenase-2 Inhibitors and Acute Myocardial Infarction in Older Adults // Circulation. 2004; 109: 2068–2073. https://doi.org/10.1161/01.CIR.0000127578.21885.3E
5. **Karateev AE** Quantitative and qualitative assessment of the risk of complications when using non-steroidal anti-inflammatory drugs as the basis for the formation of recommendations for their control and prevention. Modern rheumatology. 2014.; 1:64–72.] (In Russ).
6. Clinical guidelines for the rational use of nonsteroidal anti-inflammatory drugs (NSAIDs) in clinical practice. Sovremennaya Revmatologia. 2015; 1: 4–23.] (In Russ).
7. **Morozova TE, Shmarova DG, Rykova SM** The Choice of non-steroidal anti-inflammatory drugs in patients with rheumatological profile with concomitant cardiovascular diseases. Attending physician. 2016.; 8:7–16.] (In Russ).
8. **Sychev DA, Ignatiev IV, Kazakov RE. et all.** Pharmacogenetics in rheumatology: prospects for individualization of therapy. Scientific and practical rheumatology. 2005.; 5:59–63.] (In Russ).