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MECHANISMS OF ACTION OF NON-STEROID ANTI-INFLAMMATORY DRUGS IN THE DEVELOPMENT OF GASTROPATHY


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НОСТЕРОИД ЯЛЛИҒЛАНИШГА ҚАРШИ ДОРИЛАРНИНГ ГАСТРОПАТИЯ РИВОЖЛАНИШИНИДА ТАЪСИР МЕХАНИЗМИ

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МЕХАНИЗМЫ ДЕЙСТВИЯ НЕСТЕРОИДНЫХ ПРОТИВОВОСПАЛИТЕЛЬНЫХ ПРЕПАРАТОВ В РАЗВИТИИ ГАСТРОПАТИИ

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Резюме. *Ностероид яллиғланишга қарши дорилар (НЯҚДлар) кенг қўлланиладиган дорилар гуруҳидир. НЯҚДларни қабул қилишда муҳим муаммо бу ошқозон-ичак трактидан (ОИТ) турли даражадаги - диспепсиядан қон кетиш ёки яра тешилиши каби ҳаёт учун хавфли асоратларгача бўлган салбий дори реакйиялари булиб хисобланади. Шу жумладн айтиш керак, илмий длзарблиги ошириш янада мухимрок.*

Калит сўзлари: *НЯҚДлар, ошқозон-ичак тракти, диспепсия, қон кетиш, механизм.*

Abstract. *Non-steroidal anti-inflammatory drugs (NSAIDs) are a group of commonly used medicines. An important issue with NSAIDs is gastrointestinal (GI) side reactions at various levels, from dyspepsia to life-threatening complications such as bleeding or wound perforation. The above words confirm that this article is relevant today.*

Key words: *NSAIDs, gastrointestinal tract, dyspepsia, bleeding, mechanism.*

Introduction. The formation of the risk of developing adverse reactions of drugs can be attributed to genetic factors, in particular, polymorphism of the CYP2C9 gene. Carriers of "slow" alleles of the CYP2C9 gene (* 2, * 3) have been shown to develop more gastric bleeding when receiving NSAIDs (selecoxib, diclofenac, ibuprofen, naproxen or piroxycam) [1-3].

For the Prevention of NSAIDs from the gastrointestinal tract, proton pump inhibitor (PNI) is widely used: omeprazole, lansoprazole, raboprazole. The speed of metabolism and the effectiveness of these PNIS depend on the polymorphism of the CYP2C19 gene (* 2, * 3, * 17) [4, 5]: "in slow" alleles carriers (*2, * 3) it is higher. compared to the" wild type", in the carriers of the" fast " allel * 17, the efficiency-adorlik is significantly reduced.

Since the NSAIDs and PNI groups are often combined with drugs, it is necessary to study the genotypes CYP2C9 and CYP2C19 for the risk of complications during therapy.

The purpose of this work is to: investigate the effects of polymorphism of the genes CYP2C9 and CYP2C19 on the risk of complications of the gastrointestinal tract when taking NSAIDs and PNI.

Materials and methods: the examination was conducted in the design of a prospective clinical study of the comparative effectiveness and safety of NSAIDs in the treatment of patients with pain syndrome, to which 69 patients undergoing inpatient treatment in the Department of neurology of the branch of the Multidisciplinary clinic of the Tashkent Medical Academy are identified by examination and treatment.

We have reaped a group of patients with the pain syndrome indicated for NSAI therapy. The high percentage of drugs metabolized diclofenac, reumoksikam and meloxicam with the participation of CYP2C9 was determined. Also, these patients underwent CYP2C19 genotyping.

All patients underwent high-endoscopy and revealed Hp status by conducting a 13C-urea breath

test. Among those surveyed, 11 patients with gastropathy (15.9%) were identified, CYP 2c19 polymorphism was studied in this group of patients.

All patients were divided into two groups: 11 patients with advanced gastropathy within 2 weeks after the application of NSAI (main group); 58 patients without gastropathy who used NSAI before endoscopy (comparison group). The average admission of nyqvs was 6,2 ± 0,1 months in the group with gastropathy, and 4,9 ± 0,3 months in the group without gastropathy. The control group included 94 healthy volunteers (control group). Genotyping of the CYP 2C9 and CYP 2C19 gene was carried out by PCR-RFLP (polymerase chain reaction and limitation fragment length polymorphism). Statistical processing of the results of the study was carried out: openepi online calculator [https://www.openepi.com/TwobyTwo.htm] using. The compatibility of the observed genotype frequency distribution of genes studied in the theoretically expected control group from the Hardi-Weinberg balance was evaluated by the x2 test. The calculation was carried out using an online calculator: http: // www.oege.org/software/ hwe-mr-calc.shtml.

Results of the study: when comparing the frequencies of the genotypes of CYP2C9 in a small group of patients with gastropathy using the x2 test, the results of the study showed that CYP2C9 * 1/*2, CYP2C9 * 1/*3 and CYP2C9 * 3/* 3 genotypes have been identified. more often in patients with gastropathy than in patients without gastropathy are threeraydi: 70% V8 35%, ch2 = 14,514, p = 0,0058 (Table 1).

This indicates that there is a link between the transportation of alleles variants of CYP2C9 * 2, CYP2C9 * 3 and the development of gastropathy in patients with pain syndrome who received NSAIDs. When comparing the frequencies of the CYP2C9 genotypes in the main and control groups of patients using the X2 criteria, it was found that statistically significant differences were not found in the distribution of the CYP2C9 genotypes: ch2 = 5,315, p = 0,2565 (Table 1).

This suggests that there is no correlation between the transportation of CYP2C9 * 2, CYP2C9 * 3 allel variants and the development of the criteria of the gastro-duodenal region in patients receiving long-term NSAIDs. Considering the available data that transportation of the CYP2C9 * 3 allele variant will most likely contribute to the genetically determined decrease in the activity of the CYP2C9 isoenzyme. As a result of the study, we found that the frequency of carrying an allele of the CYP2C19 gene in patients receiving NSAIDs was 97.1%, in the control group - 98.9%. If the frequency of G allele was 2.6 times higher in patients with pain syndrome and coincided with the expected Hardy-Weinberg balance, then ch2 = 7,0, p = 0,008. The transport of heterozygous a / G allele in the CYP2C19 gene in patients receiving NSAIDs was noted in 17.4% of cases, and in controls in 2.1% of cases (Figure 1).

There was a relationship between G allele, G / G genotype and the presence of NSAIDs gastropathy at the allele and genotypic level (Table 2).

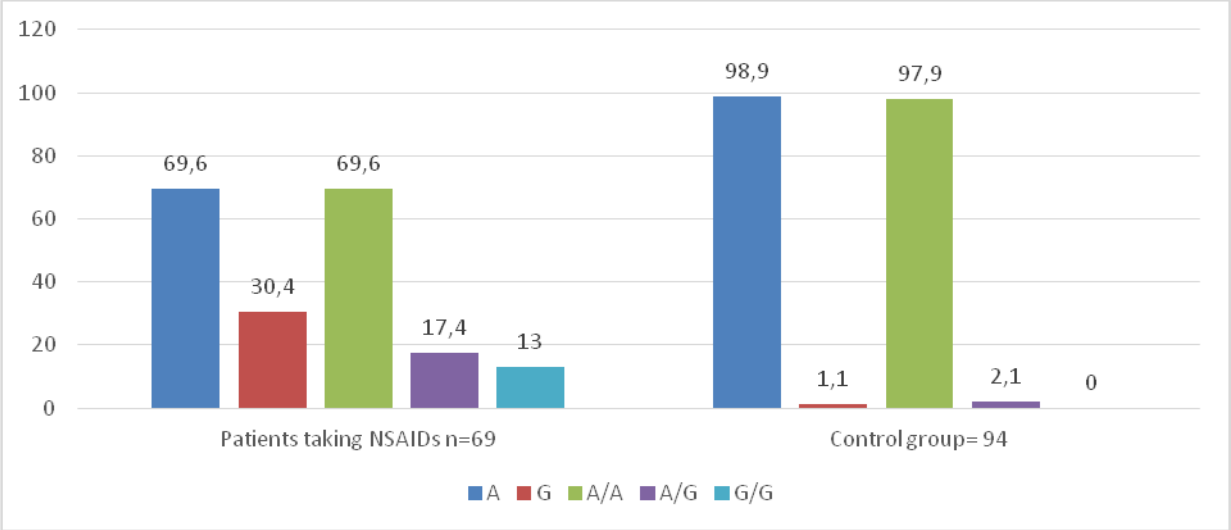
The presence of CYP 2C19 G allele is significantly associated with gastropathy provoked by NSAIDs and can be considered a risk factor for their development, which is probably explained by the participation of the isoenzyme CYP 2C19 in the metabolism of arachidonic acid, which plays a role. in gastrotsitoprotection. There is an accelerated metabolism of PNI in patients with CYP2C19 polymorphism, which significantly reduces their clinical effectiveness. Significant differences in the frequencies of alleles CYP2C9 and CYP2C19 were found between groups of patients with and without complications from the gastrointestinal tract during the reception of NSAIDs and PNI.

Conclusion. The study showed the effects of polymorphism of the genes CYP2C9 and CYP2C19 on the risk of complications of the gastrointestinal tract when taking NSAIDs and PNI. The probability of developing CYP2C9 * 3 allele carriers was statistically significantly higher in patients who did not have CYP2C9 * 3 in patients with gastropathy provoked by NSAIDs.

Table 1. Prevalence of CYP2C9 genotypes among patients with gastropathic pain syndrome caused by the use of NSAIDs

Genotype	Gastropathy +		Gastropathy -		
	Abs.	%	Abs.	%	
CYP2C9*1/*1	7	63,6	38	65,5	$\chi 2$ =2,1; p>0,05; OR=0,25; 95% CI 1,04-3,26; df=1,000
CYP2C9*1/*2	1	9,1	8	13,4	$\chi 2$ =0,180; p>0,05; OR=0,65; 95% CI 0,11-0,56; df=1,000
CYP2C9*1/*3	2	18,2	9	15,5	$\chi 2$ =0,049; p>0,05; OR=1,17; 95% CI 0,091-4,76; df=1,000
CYP2C9*2/*2	0	0	2	3,4	NaN
CYP2C9*3/*3	1	9,1	1	1,7*	$\chi 2$ =1,565; p<0,05; OR=5,27; 95% CI 0,36-78,13; df=0,315

Note: * - reliability of data between groups (P <0,01)



OR=6,9 (CI 1,44-33,0); $\chi 2$=58,8, p<0,001

Picture 1. The frequency of proliferation in patient groups depending on the sex and control of polymorphism alleles and genotypes in the CYP2C19 gene

Table 2. Determination of alleles and genotypes of polymorphism in the CYP2C19 gene, depending on the presence of gastropathies in patients with pain syndrome who received NSAIDs.

alleles/ genotype	Gastropathy + (n=11)		Gastropathy - (n=58)		
	n	%	n	%	
A	14	63,6	82	70,7	$\chi 2$ =12,1; p=0,05; OR=0,25; 95% CI 0,11-0,56; df=0,014
G	8	36,4	34	29,3	
AA	6	54,5	42	72,4	$\chi 2$ =14,2; p=0,01; OR=8,25; 95% CI 2,56-26,6; df=0,030
AG	2	18,2	11	19,0	
G/G	2	18,2	5	8,6	

The determination of the alleles variant transport of CYP2C9 * 3 predicts the development of complications in patients with gastropathy caused by the use of NSAIDs, the predictive value of a positive result is 100%, the negative - 25%.

CYP 2C19 is a common polymorphism, the carriers of which have a high metabolic rate of some drugs of clinical significance (PNI, eskitalopram, sertraline, clopidogrel, etc.), which are subsequently characterized by a decrease in their concentration in blood plasma and a weakening of clinical indicators. effect (Goldstein J.A., 2001; Ingelman-Sundberg M. et hand., 2007; Rosemary J., Edithan C., 2007; Baldwin R.M. et hand., 2008; Hunfeld N.G. et hand., 2008; Li-Wan-Po A. et hand., 2010; Pedersen R.S. et hand., 2010; Sibbing D. et hand., 2010; Scott S.A. et hand., 2012b; Zebalza M. et hand., 2012; Musumba C.O. et hand., 2013).

However, based on the review of data on the functional and clinical consequences of the transport of CYP2C19 G allele, it came to the conclusion that CYP2C19 has a small effect, which can't be clinically significant, except for CYP 2C19*. For drugs with a narrow range of "therapeutic window" - G homozygotes and only. (Ingelman-Sundberg M. et hand., 2007; Li-Wan-Po A. et hand., 2010; Scott S.A. et hand., 2012b).

On the other hand, in some recent studies, scientists have concluded that the transport of CYP2C19 allele in patients receiving clopidogrel has a lower risk of platelet reactivity, cardiovascular complications and stent thrombosis, but a higher risk of severe bleeding. (Harmsze A.M. et hand., 2012; Zebalza M. et hand., 2012).

Therefore, one of the possible explanations of the identified relationship may be that CYP 2c19 carriers have an accelerated metabolism and a decrease in the clinical efficacy of PNI, which leads to a decrease in the gastroprotic ability of the mucosa to resist aggressive factors. Thus, it is prone to the appearance of gastropathies.

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МЕХАНИЗМЫ ДЕЙСТВИЯ НЕСТЕРОИДНЫХ ПРОТИВОВОСПАЛИТЕЛЬНЫХ ПРЕПАРАТОВ В РАЗВИТИИ ГАСТРОПАТИИ

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Резюме. *Нестероидные противовоспалительные препараты (НПВП) - это группа широко используемых лекарств. Важной проблемой при приеме НПВП являются побочные реакции со стороны желудочно-кишечного тракта (ЖКТ) на различных уровнях - от диспепсии до опасных для жизни осложнений, таких как кровотечение или перфорация раны. Вышеизложенные слова подтверждают, что данная статья является актуальной на сегодняшний день.*

Ключевые слова: *НПВП, желудочно-кишечный тракт, диспепсия, кровотечение, механизм.*