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Review

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Assessment of the impact of PTGS1, PTGS2 and CYP2C9 polymorphisms on pain, effectiveness and safety of NSAID therapies

Ocena wpływu polimorfizmów PTGS1, PTGS2 i CYP2C9 na ból, skuteczność i bezpieczeństwo terapii NLPZ

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Summary

Cyclooxygenase 1 and 2 (COX-1, COX-2) are enzymes that catalyze the first reaction in the arachidonic acid pathway. COXs are the therapeutic target for non-steroidal anti-inflammatory drugs. Inhibition of COX enzymatic activity has an analgesic, anti-inflammatory and sometimes antiplatelet effect. Single-nucleotide polymorphisms (SNPs) within genes encoding COX-1 and COX-2 (PTGS1, PTGS2) influence the risk of pain and their intensity in some diseases. They also affect the effectiveness of NSAID therapy in rheumatoid diseases. Moreover, the relationship between certain polymorphisms of PTGS2 and a higher risk of migraine and the development of aspirin resistance in the prophylaxis of cardiovascular diseases was demonstrated. The isoform of cytochrome P450, CYP2C9 has a significant influence on the efficacy and safety of NSAID use. It is responsible for the metabolism and speed of removal of these drugs. The occurrence of some of its polymorphic forms is associated with a decrease in CYP2C9 enzymatic activity, leading to changes in the pharmacokinetics and pharmacodynamics of NSAIDs. The prolonged half-life and decrease in clearance of these drugs lead to serious side effects such as hepatotoxicity, nephrotoxicity, anaphylactic reactions, cardiovascular or gastrointestinal incidents. Studies on polymorphisms of cyclooxygenases and CYP2C9 may improve the safety and efficacy of NSAIDs therapy by adjusting the dose to individual polymorphic variants, as well as expanding knowledge about the pathomechanism of inflammatory diseases.

Keywords: **SNPs, COX-1, COX-2, COX-3, NSAIDs, CYP2C9, PTGS1, PTGS2, pai**

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INTRODUCTION

In the therapy of pain, non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly used. They are indicated in the therapy of rheumatoid diseases such as ankylosing spondylitis, osteoarthritis, acute edema and inflammation after trauma or surgery, cancer pain, especially with metastases to the bones, fever and in the prevention of cardiovascular events [14, 23, 38, 50, 61, 73, 75]. Short-term NSAIDs intake is even higher in musculoskeletal injuries [22, 105]. However, experiencing pain is a complex and complicated process [26, 26]. NSAIDs are most effective in the treatment of inflammatory pain [20]. This kind of pain is characterized by nociception, which is enhanced by peripheral and central sensitization. It results in higher excitability of nociceptors. Activated endothelial, stromal and immune cells release prostaglandins, cytokines and other inflammatory mediators, which contribute to peripheral sensitization by amplifying signal transduction in the peripheral terminals of nociceptors [78].

COX-1 is an enzyme encoded by PTGS1 and its constitutively expressed across different tissues [10]. The main role of this enzyme is the production of prostanoids that provide gastrointestinal protection, cytoprotection and platelet function [74]. COX-2 is encoded by PTGS2 and the expression of COX-2 takes place under the influence of stress and inflammatory factors [28]. In normal conditions, cells express a little amount to no COX-2 [10].

Additionally, the last described isoform of cyclooxygenases was COX-3 [16]. COX-3 is a splice variant of COX-1 that retains the intron-1 gene sequence at the messenger (m) RNA level [16]. COX-3 is found in the cerebral cortex and cardiac tissue and appears to be involved in centrally mediated pain. Unlike aspirin and other NSAIDs, acetaminophen produces analgesia centrally as a COX-3 inhibitor and via activation of descending serotonergic pathways [2, 30]. This particular isoform is especially sensitive to inhibition by paracetamol (acetaminophen) [2, 30].

The substrate for both COX is arachidonic acid. They catalyze the first reaction in the prostanoid synthesis pathway [17]. Both COX-1 and COX-2 have two enzymatic activities COX and peroxidase. These two distinct activities are separated by their location in the enzymes. They are on opposite sites of izoenzymes [9]. COX are involved in catalyzing two distinct reactions: the cyclooxygenation of the endogenous arachidonic (PGG2) and the formation of prostaglandin endoperoxide (PGH). As a result, a wide range of molecules (PGD2, PGE2, PGF2α, PG12 and TXA2) are formed by various PG synthases [74]. Despite having the same catalytic activities of both COX, they are differently regulated. For example, COX-1 requires higher levels of hydroperoxides to start COX catalysis than COX-2. In addition, the activity of COX-2 occurs at lower levels of free arachidonic acid than the activity of COX-1 [9]. As a result of the inhibition of cyclooxygenases, especially COX-2, prostaglandins E2, PGI2 and PGD2, which are involved in the transmission of pain reaction to the inflammation, do not form [10, 17].

The role of PGE2 in promoting peripheral sensitization and transmission of pain information has been well established [17, 31]. PGE2 exerts its effect through binding to E prostanoid (EP)1 receptors; PGI2 acts through IP receptors, and both stimulate protein kinase C (PKC)-dependent phosphorylation of TRPV1.This results in decreasing the excitatory threshold of the channels and the promotion of thermal hyperalgesia [60, 64, 66]. PKA- and PKC mediated sensitization of sodium channels leads to mechanical and also thermal hyperalgesia [25, 54, 66, 82]. PGE2 also promotes sensitization of purinergic P2X3 receptors [94], T-type calcium channels [42] and increases sensitivity of peripheral neurons to other inflammatory mediators as, e.g., bradykinin [43, 95].

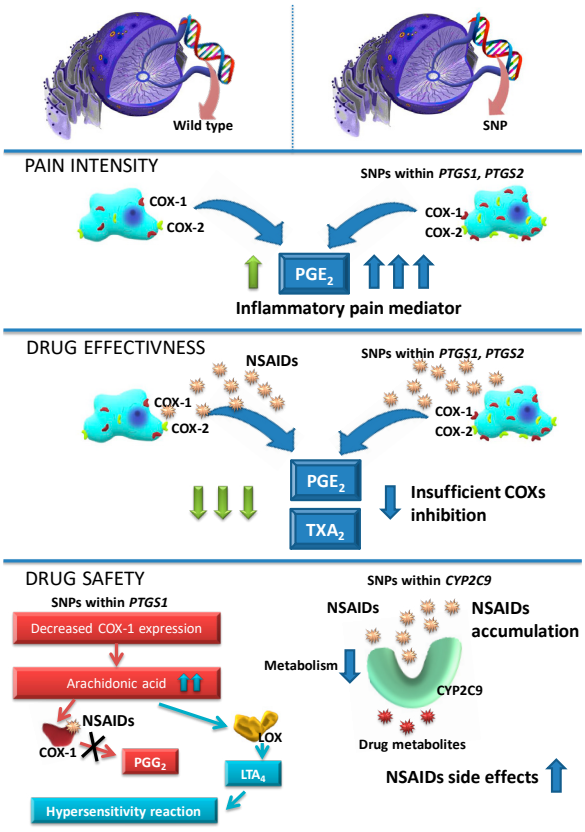

Fig. 1. Graphical abstract

SNP – single-nucleotide polymorphism; PTGS1 – prostaglandin-endoperoxide synthase 1 gene; PTGS2 – prostaglandin-endoperoxide synthase 2 gene; COX-1 – Cyclooxygenase 1; COX-2 – Cyclooxygenase 2; PGE2 – Prostaglandin E2; TXA2 – Thromboxane A2; NSAIDs –Nonsteroidal anti-inflammatory drugs; PGG2 – Prostaglandin G2; LOX –lipoxygenase; LTA4 – Leukotriene A4; CYP2C9 – Cytochrome P450 2C9 gene

Central sensitization is also partially provoked by prostanoids. Research showed that in inflammatory pain and post-operative pain, the expression of COX-1 and COX-2 in spinal cord is altered [93]. PGE2 formation in the spinal cord is increased after the systemic administration of cytokines and remains under the influence of inflammatory and nociceptive stimulation [83, 93]. PGE2 exerts its effect in the spinal cord through presynaptic stimulation:

Table 1. Impact of PTGS1 and PTGS2 polymorphisms on NSAIDs therapies

Gene	SNP	Allele	Effect	References
PTGS1	rs1236913	T	*higher pain on the first day after surgery*	75, 76
	rs10306114	G	aspirin resistance	58
	rs3842787	T	*aspirin resistance*	58
	rs1330344	G	*aspirin resistance*	64
		C	*the risk of poor functional outcomes in smokers*	65, 66, 68
	rs5789	A	*significantly higher in NERD (NSAIDs-exacerbated respiratory disease) group, decreased metabolism of arachidonic acid*	73
	rs10306135	A	*significantly higher in NERD (NSAIDs-exacerbated respiratory disease) group*	70
PTGS2	rs689466	A	*association with the risk of pain in women with endometriosis anti-migraine effect*	41, 81
		G	*decreased transcriptional activity and expression of the COX-2 enzyme increased risk of migraine, especially in patients with migraine without aura*	41, 79
	rs20417	C	*decreased transcriptional activity and expression of the COX-2 enzyme decreased production of PGE2 association with a reduced risk of migraine role in the effectiveness of aspirin therapy, aspirin resistance significantly decreased pain intensity at 48 hours after surgery after rofecoxib*	41, 42, 69, 84
	rs689465	G	*may increase the level of expression COX-2 and increase the risk of ankylosing spondylitis role in the effectiveness of NSAID treatment*	79
	rs2383515	G	*higher pain intensity on the first day after the procedure*	75
	rs5277	G	*higher pain intensity on the first day after the procedure*	75
	rs5275	T	*higher pain intensity on the first day after the procedure*	75
		C	*strongly affect the duration of COX-2 inhibition the impact on celecoxib pharmacokinetic and pharmacodynamics*	21, 71
	rs2206593	A	*higher pain intensity on the first day after the procedure*	75

it releases the excitatory neurotransmitter glutamate [70], substance P and calcitonin gene-related peptide (CGRP) from primary afferent neurons [35]. Polymorphisms within COX-2 gene contribute to the pathogenesis of migraines [21, 68]. The recently developed anti-CGRP antibody was proven to be effective in the prevention of migraine attacks [44, 84], therefore providing additional evidence for the role of inflammation in the pathogenesis of migraines [67]. Moreover, PGE2 acts in the spinal cord through EP2 receptors located on post-synaptic membrane and directly activates dorsal horn neurons [48]. This results in the reduction of descending inhibitory glycinergic currents [13, 33]. Spinal synthesis of PGI2 during the early stage of inflammation results in the recruitment GluR1 receptor membrane fraction, thereby contributing to the development of the central sensitization [85].

The efficacy of NSAIDs depends on many factors. Also, multiple factors can contribute to pain experience [52, 92]. A recent study confirmed that the regulation of the COX pathway and the inflammatory response to surgery contribute to inter-individual variability in the analgesic efficacy of NSAIDs [90]. NSAIDs are divided into selective and non-selective cyclooxygenase inhibitors. They exert their pharmacological effects by inhibiting one or both cyclooxygenases [31]. Selective NSAIDs, called coxibs, inhibit only the COX-2. Their role in pain management is controversial. Many of them had been withdrawn due to reports of high risk of cardiovascular incidents [12]. However, it seems that primarily rofecoxib (withdrawn) has been adversely affected by the risk of cardiovascular events [6]. Currently available data suggest that among patients with high gastrointestinal risk, selective COX-inhibitors should be administrated. Moreover, among patients with combined gastrointestinal and cardiovascular risk, coxibs are preferred with adjusted aspirin dose [5, 8]. Recently, one of the coxibs, mavacoxib, gained attention as a potential anti-tumor drug, given that the expression of COX-2 is elevated in many types of tumors [37]. Non-selective cyclooxygenase inhibitors, such as aspirin, diclofenac, flurbiprofen, ibuprofen, meloxicam, inhibit both COX-1 and COX-2 enzymes. NSAIDs inhibit the COX enzymatic activity by competing with arachidonic acid for the active site of the enzyme. Depending on the agent, inhibition may be reversible or irreversible. For example, aspirin acetylate the COX active site, causing irreversible inhibition, whereas the peroxidase activity remains intact [9]. Inhibition of COX decreases prostanoids formation. During trauma or inflammation, NSAIDs prevent the production of prostaglandins by COX-2 such as PGE2PGI2 and PGD2 and thus gain analgesic and anti-inflammatory effects [17]. Under a physiological condition, when the COX-1 is mainly expressed, in prevention of cardiovascular events, aspirin is used to stop the formation of thromboxane (TXA). TXA facilitates platelet aggregation and thus thrombus formation [100].

Findings of functional polymorphisms in genes that encode cyclooxygenases may improve the safety and efficiency of NSAIDs therapies by allowing for better adjustment of drug dose depending on individual gene variants of patients. Moreover, the polymorphisms of COX-1 and COX-2 have showed a moderating influence on experienced pain level and susceptibility to inflammatory diseases [21, 96]. Numerous studies have demonstrated the correlation of cyclooxygenase polymorphisms with the incidence of neoplastic, neurodegenerative disease as e.g. Alzheimer's disease, autoimmune and inflammatory diseases [1, 51, 58, 69, 76, 79]. The aim of the paper is to present polymorphisms within genes encoding both COX and isoform of cytochrome P450 CYP2C9, which are likely to influence and account for the inter-individual variation in pain perception and the effectiveness of pain and inflammation treatment with non-steroidal anti-inflammatory drugs.

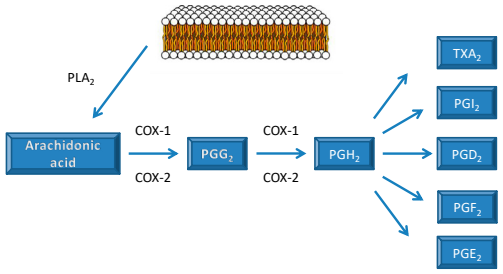

Fig. 2. Arachidonic acid pathway

PLA_2 - Phospholipases A2; COX-1 - Cyclooxygenase 1; COX-2 - Cyclooxygenase 2; PGG2 - Prostaglandin G2; Prostaglandin H2; TXA2 - Thromboxane A2; PGI2 - Prostacyclin; PGD_2 - Prostaglandin D2; PGF_2 - Prostaglandin F2; PGE_2 - Prostaglandin E2

POLYMORPHISMS OF *PTGS1* AND *PTGS2*

PTGS1

The PTGS1 gene is located on chromosome 9 and contains 11 exons. The product of its expression is cyclooxygenase 1, an enzyme present constitutively [28].

rs10306114, rs3842787

The polymorphisms rs10306114 (-842G) and rs3842787 (50T) were reported to have an effect on aspirin resistance (AR) [62]. Aspirin was one of the first drugs invented which belonged to the group of NSAIDs [86]. Moreover, it is one of the most commonly used drugs worldwide in the prevention of cardiovascular events [7, 15]. Effectiveness of aspirin in the prevention of thromboembolic events consists in inhibiting platelet aggregation as a result of COX-1 inhibition and inhibition of TXA2 production [100]. The studies indicate that some of the patients are resistant to antiplatelet effect of aspirin, which results in higher amount of cardio- and cerebrovascular events [7]. In order to investigate the genetic resistance, PTGS1 polymorphisms were verified. A meta-analysis revealed no significant association between rs10306114 and rs3842787 and aspirin resistance; however, the number of studies was limited and the methodology differed between them [29]

rs1330344

Nevertheless, another polymorphism, rs1330344, showed an association with aspirin resistance, according to a study on 431 Chinese patients. Rs1330344 is located in the promoter region of COX-1 gene and its functional consequence is to form the upstream transcript variant. The carriers of the G allele have a significantly increased risk of AR (OR = 1.77) [55]. Several studies have fueled the association between smoking and lack of response to aspirin [18, 59]. The cause may lie in elevated COX-1 expression due to up-regulation of COX-1 pathway [57]. A study conducted among 617 Chinese patients who suffered from ischemic stroke has confirmed a potential contribution of rs1330344 polymorphisms in the development of aspirin resistance. The correlation was particularly clear in the group of patient who admitted to smoking. The risk of poor functional outcomes was the highest in smoking patients with CC genotype, presenting a 3.05-fold increased risk in comparison to non-smokers with CT/TT genotype. Moreover, interaction analysis revealed that interaction between rs1330344 and smoking status was significant [11]. Meta-analysis confirmed the relation of this polymorphism with poor responsiveness to aspirin [102].

rs5789

Rs5789 polymorphism showed a correlation with the exacerbation of respiratory diseases after NSAIDs intake [4]. Currently, NSAIDs are the most frequently involved drugs in hypersensitivity drug reactions (HDRs) [24]. According to recent studies, NSAIDs-exacerbated respiratory disease (NERD), previously known as ASA-induced asthma, is partially dependent on polymorphisms within PTGS1 gene. It is claimed that cyclooxygenase-1 (COX-1) inhibition shunts the arachidonic acid metabolism towards the synthesis of cysteinil-leukotrienes, which in turn elicit a reaction in susceptible individuals [24, 41]. The study included total of 250 NERD patients, 260 NSAID-tolerant asthmatic (NTA) patients and 315 unrelated healthy subjects. The frequency of allele A was significantly higher in NERD group, and the AA homozygotes were the most likely to develop hypersensitivity reaction. The A allele of rs5789 polymorphism is associated with decreased metabolism of arachidonic acid [32], which, with further inhibition of COX-1 activity by NSAIDs intake, could lead to the overproduction of leukotrienes and NERD development [41].

rs10306135

Another polymorphism, which was evaluated within the context of NERD induction, is rs10306135 [4]. This SNP is located close to the promoter region of PTGS1 [34], but its exact impact on PTGS1 expression remains unknown and requires further studies. The A allele of rs10306135 was associated with NERD with OR: 1.73 and the AA homozygous with OR: 2,12 [4].

rs1236913

Applebaum et al. [3] observed variability in the perception of pain before and after surgery among patients undergoing root canal treatment. These differences were related to the modulating effect of PTGS1 and PTGS2 gene polymorphisms. In this study, a number of PTGS2 polymorphisms which correlate with the increased pain perception of patients were identified. Among polymorphisms of the PTGS1 gene, the T-allele rs1236913 showed a positive correlation with greater intensity of pain on the first day after surgery. This polymorphism is located on exon 2. It causes amino acid change from tryptophan to arginine in 102 codon. This mutation has also been associated with a more severe course of ankylosing spondylitis (AS) [3, 19].

PTGS2

COX-2 is encoded by PTGS2, a gene present on chromosome 1 and containing 10 exons [28].

rs2383515, rs5277, rs2206593, rs5275

The authors observed the association of the G rs2383515 allele, G rs5277, T rs5275 and A rs2206593 with a higher pain intensity on the first day after the procedure. These 4 polymorphisms remained in strong linkage disequilibrium (D '= 0.99–1) and formed a haploblock consisting of 1 SNP in the promoter region (rs2383515 G/T), 1 SNP in the coding region (rs5277 C/G), and 2 SNP in part 3 'UTR (rs5275 C/T and rs2206593 A/G). The GGTA haplotype was associated with the occurrence of the most severe pain a day after surgery (p = 0.025) [3].

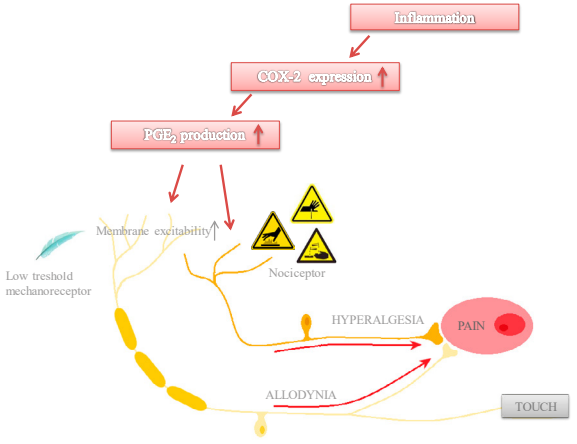

Fig. 3. Mechanism of inflammatory pain

rs5275

The impact of rs5275 polymorphism on celecoxib pharmacokinetics and pharmacodynamics was assessed by Lee et al. [52]. These polymorphisms strongly affect the

duration of COX-2 inhibition. To assess the inhibition of COX-2, PGE2, the plasma level was measured after a single oral dose of 200 mg of celecoxib. This effect was observed among CC homozygous; however, the number of subjects was very limited (n = 1, subjects with CC genotype) and, therefore, this finding needs to be confirmed by further studies comprising larger sample size [52]. The C allele of this SNP interferes with miR-542-3p function promoting overexpression of COX-2 [65], although there are some contradictions in the obtained data with regard to the exact role of this SNP on the COX-2 level [27].

rs689465

The next discussed polymorphism is PTGS2 -1290 A/G (rs689465) and it remains in strong linkage disequilibrium with the polymorphism rs689466, the occurrence of which may increase the level of expression COX-2 and increase the risk of ankylosing spondylitis. In this way, rs689465, although it does not show any functionality, may affect the course of AS and the effectiveness of NSAID therapy. The polymorphic variant G rs689465 in people with AS has a higher frequency, compared to healthy individuals. In the BASDAI tests performed in people with AS before the treatment, people with the G allele received higher scores and their symptoms were more severe, compared to AA homozygotes. After 12 weeks of NSAID therapy and BASDAI reassessment, patients with the G allele achieved lower scores, compared to those who did not have this allele, suggesting an effect of this polymorphism on the effectiveness of NSAID treatment [98].

rs689466

In the same study as rs5275, rs689466 was also evaluated. This SNP also affects the pharmacodynamics of celecoxib. AUEC (area under the effect curve) rs689466 GG genotype was much lower than for AA or AG genotype, suggesting that the individuals with GG genotype would be more sensitive to NSAIDs inhibiting COX-2 [52].

The polymorphism of rs689466 also plays a role in the efficacy of NSAID therapy. In ankylosing spondylitis (AS) and other inflammatory and autoimmune diseases, NSAIDs are one of the basic pillars of pharmacotherapy. NSAIDs inhibit the activity of cyclooxygenases and block the synthesis of prostaglandins and thus contribute to the reduction of symptoms, such as fever, pain, inflammation, rheumatism and platelet aggregation [80]. A study of 130 Chinese patients with AS, who were receiving 12-week NSAIDs therapy, showed a significant reduction of symptoms. In addition, in the study group, the incidence of variant A polymorphism rs689466 was significantly higher, compared to the control group. Persons with the GG genotype achieved prior to the start of treatment higher average results of the BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) test than patients with GA and AA genotypes. The results of BASDAI after 12 weeks of therapy were lower than 4 in both groups; however, in the homozygote group, GG remained higher than in people with the A allele. Obtaining such data indicates the influence of rs689466 polymorphism on the effectiveness of NSAID therapy [98].

Moreover, polymorphism rs689466 is associated with the risk of pain in women with endometriosis. A significantly higher frequency of both AA homozygotes and A-alleles was observed among patients in the study group, compared to the healthy control group. Among women who were in the group experiencing severe pain, a significantly higher frequency of AA genotype was observed, compared to women in the group experiencing moderate and mild pain. These studies suggest that the rs689466 polymorphism in the COX-2 gene promoter region may increase the risk of pain occurrence [96]. The polymorphism of rs689466 in the COX-2 promoter region generates a c-MYB binding site, and the presence of the A-allele may increase the COX-2 transcriptional activity and increase the susceptibility to endometriosis [36].

RS689466 AND MIGRAINE

Physiologically, COX-2 expression occurs in the spinal cord and forebrain [101]. Currently, it is thought that migraine pain is associated with an increase in brainstem activity, which is attributed to the likely role of a migraine attack generator. Another reason for migraine is connected with genetic conditioning for hyperactivity of neurons in the pathomechanism of migraine [103]. According to the theory of neural tissue inflammation, it is suggested that the development of sterile inflammation is the cause of migraine. It is associated with an increase in the secretion of inflammatory mediators, including products of transformation of arachidonic acid, through the vascular endothelium of the meninges of the brain [67]. In Turkey, a higher level of COX-2 expression was more likely to be found in the migraine population than in the healthy subjects. The selected polymorphisms of the COX-2 gene were examined in the group of patients with migraines and the frequency of their occurrence was compared among healthy controls. The following polymorphisms were taken into consideration: COX-2-1195A → G (rs689466), COX-2-765 G → C (rs20417) [21].

In previous studies analyzing rs689466, the G allele of the COX-2 gene promoter was associated with decreased transcriptional activity and decreased expression of the COX-2 enzyme. Dasdemir et al. [2] demonstrated that the AG genotype has a protective effect against migraines. The presence of GG genotype correlates, in turn, with an increased risk of migraine, especially in patients with migraine without aura. The results concerning rs689466 polymorphism showed that the AA genotype (wild type) was statistically more frequent in the control group, which determines the reduction in the risk of a migraine attack. The frequency of GG and AG genotypes among

patients was higher than in the control. In the Turkish study, the genotype PTGS2 rs689466 AG was associated with a protective anti-migraine effect, and in the Iranian study, with an increased risk of migraine, also attributing the risk-reducing effect to the genotype rs689466 AA. The ambiguity of the results indicates a need for further research in this area [21, 68].

RS20417 AND MIGRAINE

In the case of polymorphism COX-2-765 G → C (rs20417), in the control group the frequency of occurrence of the rs20417 C genotype was higher, compared to the study group (57.7% and 36.1%, respectively). In the group of patients with migraine, the frequency of the genotype rs20417 G + was higher, compared to the control group (97.7% and 88.6%, respectively). Similarly, rs20417 genotypes GG and GC occurred more frequently in patients than in the control group. The CC genotype correlates with a reduced risk of migraine. It is assumed that the polymorphism of rs20417 CC within the COX-2 gene promoter, reduces the expression level of this gene, and consequently reduces the production of PGE2, which is a mediator of inflammatory pain. The presence of the rs20417 GG and GC genotype is associated with higher COX-2 gene promoter activity with higher COX-2 expression levels and increased PGE2 production. [21] In an Iranian study, they evaluated the risk of migraine in PTGS2 polymorphisms. The frequency of rs20417 CC and GC genotype was significantly higher in the migraine patients. The wild type rs20417 GG was significantly more common in the control group. There were no significant differences in the distribution of rs20417 CC genotype and the GC between the migraine-aura and migraine without aura [68].

rs20417

Lee et al. [53] investigated the influence of rs20417 on rofecoxib and ibuprofen efficacy after a minor surgery. The presence of G allele of this polymorphism correlated with a higher level of PTGS2 expression. Forty-eight hours after treatment, the patients showed a significantly different analgesic response to the non-selective COX inhibitor (ibuprofen) and the selective COX-2 inhibitor (rofecoxib) depending on their functional polymorphisms in PTGS1. Patients who were CC homozygous experienced significantly decreased pain intensity at 48 hours after surgery after rofecoxib, but not after ibuprofen administration. However, patients who were minor allele carriers homozygous and heterozygous (CC and GC) for rs20417 had an adverse effect after 48 hours, showing significantly reduced pain intensity in response to ibuprofen, but not after rofecoxib intake [53].

Polymorphism rs20417 plays an important role in effectiveness of aspirin therapy as well. In a study conducted in the Chinese population, it was demonstrated that in a group of people resistant and moderately resistant to aspirin, the frequency of polymorphism in the PTGS2 gene rs20417 was significantly higher, compared to the group of people sensitive to aspirin.

All patients (n = 360) received aspirin at the beginning of the study regardless of their belonging to a particular group of aspirin sensitivity. After an average of 24 months, a significantly higher frequency of cardiovascular and cerebrovascular events was observed in the group of aspirin resistant and semi-resistant people, compared to the aspirin-sensitive group. A meta-analysis conducted by Weng et al. [99] and Yang et al. [102] confirm the role of polymorphism C rs20417 in the emergence of aspirin resistance. In addition, more frequent occurrence of this mutation in the Chinese population, compared to the Caucasian population, was proved. The need to construct databases for genes and polymorphisms suspected to be responsible for aspirin resistance for every race and ethnic group is suggested [99], as different populations may have different, specific to themselves, patterns of inheritance of genes, which remain in linkage disequilibrium [71].

CHARACTERISTICS OF CYP2C9

CYPC29 is the main isoform of cytochrome P450, which is involved in the oxidation of xenobiotics and endogenous substances in the body. It is encoded by a gene located on the chromosome 10. It is produced mainly in the liver, constituting 20% of all CYP proteins present in hepatocytes microsomes [81] and its expression level is the second highest after CYP3A4. It has been estimated that CYPC29 is responsible for the metabolism of many clinically important compounds, including non-steroidal anti-inflammatory drugs such as: Celecoxib, Diclofenac, Ibuprofen, Lornoxicam, Meloxicam [91]. The occurrence of many CYPC29 polymorphisms explains the difference in the organism's response to analgesic therapy and the variable severity of adverse reactions resulting from the use of non-steroidal anti-inflammatory drugs [40].

Distribution of CYP2C9 polymorphisms varies depending on the ethnic group. The CYP2C9 *1/*1 genotype is found in 75% of Caucasians, the remaining 25% have genotypes: CYP2C9 * 1/* 2 and CYP2C9 *1/*3, less than 2.5% of the population has a carrier of genotypes: CYP2C9 * 2/* 2, CYP2C9 *2/*3 and CYP2C9 *3/*3 [72]. Polymorphism rs1799853 occurs mainly in Caucasians (16%), while rs1057910 occurs in about 3–8% of Caucasians and in 4.5% of Asian population [49]. Polymorphismrs28371685 was identified only in the Tibetan population [56]. The analysis of the frequency of CYP2C9 alleles occurrence using an extended genotypic panel conducted on 30 African-American pediatric patients suffering from sickle cell disease using non-steroidal anti-inflammatory drugs in the analgesic therapy proved that in this population it is the most common allele appearing in addition to wild type CYP2C9 *1 (0.850) is CYPC29 *8 (0.067); the next frequently-appearing allele was CYP2C9 *5 (0.033) [40].

CYP2C9 POLYMORPHISMS

The first discussed polymorphism is rs1057910, occurring in two variants. Rs1057910 (A) encodes isoleucine at position 359; the resulting allele is referred to as CYP2C9 *1, or A. Polymorphism rs1057910 (C) is responsible for the formation of the allele referred to as CYPC29 *3, or C [87]. It involves the transition of the adenine to the cytosine at position 1075, which consequently leads to a change in the amino acid sequence through replacing the isoleucine with leucine. This results in blocking the binding site with the substrate by side chains, which leads to the reduced interaction of CYP2C9 with the drug [104]. Studies conducted on a group of 112 healthy volunteers showed that this polymorphism has the greatest influence on the pharmacokinetic parameters of S-ibuprofen.

Ibuprofen occurs in the form of 2 enantiomers: S-ibuprofen and R-ibuprofen, the S enantiomer is characterized by greater pharmacological activity; its metabolism is complex and involves oxidation by CYPC29 and glucuronidation by UGT2B7. The form of R-ibuprofen has the ability to invert to S-ibuprofen and its metabolism is preceded by an inversion step into the S-form. The analysis of the above studies showed that the occurrence of the C allele significantly affected the impairment of ibuprofen metabolism by increasing AUC, Cmax, T0.5 and reducing clearance of S-ibuprofen and R-ibuprofen in reference to the wild-type subjects [72]. In addition, another study of 21 healthy volunteers showed a 50% reduced clearance of ibuprofen among carriers of two C alleles, compared to wild type homozygotes [46].

M. Zhang et al. [25] in a study conducted among 24 volunteers from China also proved that the polymorphism of rs1057910 plays an important role in the metabolism of drugs. It leads to the significant reduction in the interaction between CYPC29 and the meloxicam-non-steroidal anti-inflammatory drug used to treat rheumatoid arthritis [104]. The assessment of the effect of A/C and C/C genotypes on pharmacokinetics and pharmacodynamics of meloxicam in healthy Korean volunteers showed that there is a relation between C/C genetic carrier involvement and increased exposure to side effects due to the long-term use of this drug at standard doses. Serious side effects resulting from taking meloxicam include hepatotoxicity, nephrotoxicity, anaphylactic reactions, cardiovascular or gastrointestinal incidents, but most often diarrhea, indigestion and upper respiratory tract infections. The mean AUC results for individuals with the C/C genotype were 8.2 and 4.7 times higher than for A/A and A/C. The average half-life (T0.5) of meloxicam in individuals with the C/C genotype was 5.9 and 3.5-fold higher, compared to the A/A and A/C individuals. In subjects with the C/C genotype, there was a decrease in clearance of this drug by 11% and 21%, compared to the A/A and A/C carriers. Information on the impact of the homozygous C/C variant on meloxicam pharmacokinetics and pharmacokinetics is limited due to the low frequency of this genotype in the population (0.1% among the population of East Asia) However, the research suggest that people with this genotype may be more exposed to adverse effects resulting from long-term treatment with meloxicam due to a significant reduction in clearance and an increase in AUC and T0.5 of this drug [49].

Another study conducted in the Asian population to determine the effect of rs1057910 polymorphism on the pharmacokinetics of celecoxib, a selective COX-2 inhibitor used in the treatment of post-operative pain, rheumatoid arthritis or osteoarthritis, has shown that heterozygous A/C individuals had higher AUC (1.63 fold increase), Cmax (increase of 32.3%), less clearance (decrease by 39.6%) in the comparison to individuals with A/A genotype. Moreover, in the research group, there were homozygous C/C CYPC29 *3/*3 individuals. However, the small group size (n = 2) did not allow the result to be considered statistically significant. Substantially higher values of AUC, T0.5 and much lower clearance for celecoxib, compared to those of genotype A/A and A/C have been recorded among those patients. These results may suggest that the application of this drug for patients with the C/C genotype may result in prolonged therapy, exposure time and increased risk of side effects [45].

Studies on the influence of CYPC29 polymorphism on changes in pharmacokinetic and pharmacodynamic parameters of celecoxib, determining the concentration of this drug and its main metabolites – hydroxycelecoxib and carboxycelecoxib – by means of liquid chromatography showed an over 2-fold decrease in the clearance of this non-steroidal anti-inflammatory drug and a 3-fold increase in AUC in homozygote C/C, compared to people with the A/A genotype. Moreover, homozygous (C/C) and heterozygous (A/C) patients have a lower concentration of metabolites of celecoxib, which indicates reduced metabolism of this drug in this group [47]. A further analysis of the effect of CYPC29 polymorphism on the pharmacokinetics of celecoxib and its two major metabolites of hydroxycelecoxib and carboxycelecoxib, performed on 51 healthy volunteers proved that the rs1057910 polymorphism decreases CYPC29 activity and increases patients' exposure to this drug. In heterozygotes A/C-AUC, Cmax and T0.5 increased in turn by: 90.6%, 45.8% and 21.8% in comparison to A/A homozygotes, while the clearance of celecoxib decreased by 51.1%. In the carriers of the A/C genotype, Cmax of celecoxib decreased by 17.2%, while T 0.5 increased by 42.1%; also, a 16.1% increase in T 0.5 of carboxycelecoxib was observed, compared to the A/A homozygotes. In addition, a positive correlation was found between the existence of higher Cmax and AUC values and the occurrence of an increased number of adverse reactions [56].

The next discussed polymorphism is rs1799853, responsible for the formation of the CYPC29 * 2 allele, also called the T allele, which is based on the transition of the cytosine to the thymine at position 430, which results in the mutation of the sense change, involving replacing the cysteine with arginine [88]. A study conducted among 165 patients in the African-American population

suffering from sickle cell disease proved that the combination of CYP2C9 *2 alleles rs1799853 and CYP2C8 *3 polymorphisms rs10509681 revealed a significant impairment of ibuprofen clearance and analgesic defect [39]. Other studies have shown the connection of rs1799853 polymorphism with the decrease in the metabolism of flurbiprofen, piroxicam and tenoxicam [88]. Martinez et al. [31] described the relationship between rs1799853 and rs1057910 polymorphism with the increase of 2.5 times of the risk of gastric bleeding after NSAID therapy [63]. Pilotto et al. [32] in their work drew attention to the much more frequent occurrence of gastric and duodenum bleeding episodes during the use of NSAIDs in patients with genotype A/C (rs1057910) or C/T (rs1799853) [77].

The polymorphism rs72558187 involves the transition of the thymine to the cytosine at position 269. It generates a conformational change, directing the side chains into the binding between the substrate and the enzyme and thus limiting the interaction of these molecules. It is a rare (0.2–1%) variant of the CYPC29 gene, most common in the Asian population and due to such low incidence, it is difficult to analyze its impact on the pharmacodynamic and pharmacokinetic parameters of CYPC29 substrates. The studies in Asian population showed that individuals having a CC genotype displayed an increase in AUC and Cmax and a decrease in clearance of celecoxib, compared to individuals with wild-type genotype [45].

Li Wang et al. [97] provided interesting information by analyzing the effect of CYP2C9 polymorphism on flurbiprofen metabolism *in vitro*, using recombinant human microsomes from Sf21 insect cells. For the 36 analyzed CYPC29 isoforms found in the Chinese population, the majority reduced internal clearance of flurbiprofen, while CYPC29 *56 and CYPC29 *53 isoforms caused the increase of the CYPC29 enzymatic activity, compared to the wild-type; the flurbiprofen clearance was successively higher: 197%, 134% [97].

The allelic variants of the CYP2C9 gene play a significant role in the toxicity and generation of side effects by NSAIDs. The analysis of the genetic profile of patients undergoing treatment with these drugs would allow us to identify patients with impaired ability to metabolize them by CYP2C9, and determine the appropriate dose of the drug to achieve a satisfactory analgesic effect and to avoid side effects [40].

Table 2. Impact of CYP2C9 polymorphisms on NSAIDs therapies

Gene	SNP	Allele	Effect	References
CYP2C9	rs1057910	C	*increased exposure to side effects due to the long-term use of meloxicam at standard doses* *a significant reduction in clearance, and an increase in AUC and T0.5 of meloxicam* *reduction in clearance, increase in AUC, Cmax, T0,5 of celecoxib* *more frequent occurrence of gastric and duodenum bleeding episodes during the use of NSAIDs in patients with genotype A / C*	92, 93, 94, 96, 100, 101
	rs1799853	C/T	decreased metabolism of flurbiprofen, piroxicam and tenoxicam increased risk of gastric and duodenum bleeding after NSAID therapy	31, 98, 100, 101
	rs72558187	C	*increased AUC and Cmax and the decrease in clearance of celecoxib*	96

CONCLUSION

The purpose of cyclooxygenases is to metabolize arachidonic acid and allow its further transformation into prostaglandin (PG), prostacyclin (PGI2) and thromboxane A2 (TXA2). Due to the induction of COX-2 expression under the influence of proinflammatory cytokines and the role of arachidonic acid metabolism in the development of inflammation and inflammatory pain, changes in its structure and expression may lead to greater susceptibility to the development of inflammatory diseases. Moreover, inappropriate pain management, due to undervalued doses of NSAIDs, may lead to persistent changes in neuronal pain pathways. Obviously, PTGS1 and PTGS2 genes are not the only ones to investigate in searching for the reason for inter-individual variety of pain sensation, but they may be partially responsible for it [89]. In addition, the occurrence of PTGS1 and PTGS2 polymorphisms leading to higher expression of COX-1 and COX-2 consequently causes resistance to aspirin in the prevention of cardiovascular and cerebrovascular diseases. Therefore, people in this group could potentially benefit from adjusting the individual dose of the drug depending on the polymorphic variants possessed. Furthermore, appropriate adjustment of dose is crucial in pain management in the usual proceeding requiring several interventions of switching drugs. During that process patients continue to suffer and that could affect their mental and physical health. Although the influence of the polymorphisms on the aspirin effectiveness has been well studied, the other

NSAIDs still require further research. There are only several studies that cover the area of PTGS1 and PTGS2 SNPs impact on the effectiveness and safety of NSAIDs administration. Only a few studies included, e.g., ibuprofen, celecoxib and rofecoxib. The effectiveness of ibuprofen and rofecoxib depends on the polymorphism and, therefore, indicates the need to conduct studies that include each of the NSAID. Moreover, certain SNPs lead to the hypersensitivity reaction after NSAIDs intake, thus influencing their safety. Better knowledge of CYP2C9 polymorphisms in patients receiving NSAID treatment may allow us to individualize the pharmacotherapy and improve the safety of this group of drugs. CYP2C9 polymorphisms and their influence on NSAIDs efficiency and safety have been much better studied, compared to the SNPs within PTGS1 and PTGS2 genes. However, taking into consideration the large number of polymorphic variants of CYP2C9, further research is needed for each population. A part of the identified polymorphisms is correlated with the specific drug effects only in Asian populations, whereas the same associations are not to be observed in Caucasians [52]. This is most likely the result of the existence of separate genetic inheritance patterns [99]. This indicates the need to conduct research on polymorphisms in each population, taking into account the region and ethnicity [52, 99].

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