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The Effect of Polymorphisms in the CYP2D6 and CYP2C9 Genes on the Clinical Efficacy of Tramadol and Ketorolac When Using the Accelerated Recovery Protocol in Patients with Uncomplicated Acute Calculous Cholecystitis Who Underwent Cholecystectomy

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RELEVANCE One of the key components of the accelerated recovery protocols (ARP), in addition to minimizing the surgical approach, is an adequate postoperative analgesia. Despite this, applied postoperative analgesia combinations are not devoid of drawbacks, such as lack of effective postoperative analgesia and the presence of side effect. The use of a pharmacogenetic approach to analgesic therapy for the purpose of its personalization may increase the effectiveness and safety of the use of analgesics. In particular, the presence of an inactive CYP2D6*4 allele, in which the conversion of tramadol to its active metabolite is reduced, contributes to the insufficient efficacy of the drug. As for non-steroidal anti-inflammatory drugs, the presence of CYP2C9*2/*3 polymorphisms leads to a decrease in drug metabolism and a longer half-life, resulting in the increase of the clinical effect and the risk of adverse reactions. Thus, genotyping of patients with the determination of the presence of specific genetic factors can rationalize the postoperative analgesia.

AIM OF STUDY Evaluation of the possible association of polymorphisms of the CYP2D6 and CYP2C9 genes with the clinical efficacy of tramadol and ketorolac in relation to postoperative pain.

MATERIAL AND METHODS This observational clinical study involved 107 patients with uncomplicated acute calculous cholecystitis who underwent videolaparoscopic cholecystectomy and perioperative treatment according to ARP. All patients underwent whole blood sampling followed by real-time polymerase chain reaction genotyping. Analgesic efficacy was assessed using a visual analog scale (VAS) and McGill Pain Questionnaire.

RESULTS In CYP2D64* carriers pain was higher than that of wild-type carriers, according to VAS and McGill Pain Questionnaire in all investigated periods. In carriers of CYP2C9*2, the pain syndrome was lower than in carriers of the wild type at all intervals studied. In carriers of CYP2C9*3 pain was lower only after 2 and 6 hours, also according to McGill Pain Questionnaire.

Conclusion 1. The presence of the polymorphic marker CYP2D6*4 may reduce the efficacy of postoperative tramadol analgesia compared with wild type. 2. The presence of the polymorphic marker CYP2C9*2 and CYP2C9*3 may increase the efficacy of ketorolac pain relief compared to wild type.

Keywords: tramadol, ketorolac, videolaparoscopic cholecystectomy, CYP2D6, CYP2C9, Cytochrome P 450, pharmacogenetics, ERAS

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Conflict of interest Authors declare lack of the conflicts of interests

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VAS – visual analogue scale
VLCE – video laparoscopic cholecystectomy
GIB – gastrointestinal bleeding
NSAIDs – non-steroidal anti-inflammatory drugs
ARP – accelerated recovery protocol
PCR – polymerase chain reaction
ASA – American Society of Anesthesiologists
ERAS – Early Rehabilitation after Surgery
FTS – Fast-Track Surgery

INTRODUCTION

One of the key factors in the concept of accelerated recovery is adequate postoperative pain relief [1, 2], which helps to reduce postoperative surgical stress, shorten hospital stay and increase the effectiveness of patients treatment. [3]. In the heyday of personalized medicine, an increase in interdisciplinary interaction, scientists - geneticists are actively interested in the issue of the influence of the genotype on the effectiveness and safety of drugs used in clinical practice. In particular, it turned out that the effectiveness of painkillers, as well as the risk of developing adverse reactions, are closely related to the patient's genetic characteristics [4, 5]. Genes with the help of enzyme systems affect the metabolism of drugs in the body; for example, the cytochrome P450 family affects the pharmacokinetics of drugs by altering the dose-to-drug serum concentration relationship [4]. Thus, the use of pharmacogenetic testing will make it possible to give recommendations on how to prescribe the optimal drug in the optimal dosage for each individual patient, based on a person's unique genetic profile [6, 7].

Tramadol, which is actively used as a drug for postoperative pain relief, is metabolized by the CYP2D6 gene [8]. In a study evaluating the effect of the polymorphic marker CYP2D6*4 on the effectiveness of tramadol therapy, it was noted that the frequency of the lack of effect from therapy in the presence of this polymorphism was 4 times higher compared to other genotypes [9]. A pain assessment study in CYP2D6*4 carriers reported that the visual analogue scale (VAS) showed that their pain was more intense compared to normal and rapid metabolizers [10]. Similar results were shown in the study of O. Slanar et al., 2012 [11]. With regard to non-steroidal anti-inflammatory drugs (NSAIDs), literature data indicate that carriers of the CYP2C9*2 and CYP2C9*3 alleles have a decrease in drug metabolism and a longer half-life, which increases the risk of adverse reactions from NSAIDs, in particular, gastrointestinal bleeding (GIB) [12, 13]. Thus, in a study to study the metabolism of flubiprofen depending on the polymorphisms of the CYP2C9 gene, it is reported that the clearance of the drug in carriers of the CYP2C9*1/3 polymorphism was significantly lower than in carriers of CYP2C9*1/1 and CYP2C9*1/2 [14]. Similar results have been demonstrated in the study of lornoxicam [15] and piroxicam [16]. Taking into account the relevance of the topic and the practical need for its solution, we have defined the goal and objectives.

GOAL AND TASKS

The aim of the study was to assess the possible association of CYP2D6 and CYP2C9 gene polymorphisms with the clinical efficacy of tramadol and ketorolac in relation to postoperative pain.

Based on the goal, the following tasks were set before us:

1. Compare the intensity of the pain syndrome (according to the results of the VAS and the McGill scale) depending on the presence or absence of the genotype in patients CYP2D6*4.

2. Compare the intensity of the pain syndrome (according to the results of the VAS and the McGill scale) depending on the presence or absence of the CYP2C9*2 genotype in patients and CYP2C9*3.

MATERIAL AND METHODS

This study was approved by the Research Ethics Committee of the Russian Medical Academy of Continuing Professional Education of the Ministry of Health of Russia (Protocol No. 10 of December 19, 2017). This observational clinical study enrolled 107 patients with uncomplicated acute calculous cholecystitis who underwent video laparoscopic cholecystectomy and perioperative treatment according to an optimized accelerated recovery protocol (FTS/ERAS). Informed consent to participate in this study was signed by all participants. All patients were comparable in age, sex, time of surgery, presence of concomitant pathology, time from the onset of the disease to surgery. Whole blood was taken from all patients during hospitalization, followed by genotyping using polymerase chain reaction (PCR) in real time. The distribution of groups of patients is presented in table. 1. Anesthetic efficacy was assessed using the VAS at 2, 6, 12, 24, 36, 48 hours and the McGill pain questionnaire.

CRITERIA FOR INCLUSION OF PATIENTS IN THE STUDY

The study included patients with uncomplicated acute calculous cholecystitis aged 18 to 85 years, without severe concomitant pathology (anesthetic risk according to ASA I – II), weighing 45 to 110 kg, with a period from the onset of the disease to surgery no more than 72 hours. Also, a contraindication to participation in the study was the presence of allergies to tramadol and ketorolac, previous operations on the upper part of the abdominal cavity (Table.1).

PATIENT MANAGEMENT DURING THE PERIOPERATIVE PERIOD

All surgeries were performed between September 2017 and August 2019 after ethical approval and the signing of an informed consent. All patients underwent surgery using video laparoscopic access only.

MANAGEMENT OF PATIENTS ACCORDING TO THE OPTIMIZED ARP:

— no premedication;

— preoperatively, 30 minutes before the operation, antibiotic prophylaxis with ceftriaxone 1.0 was performed intravenously once;

— drainage of the abdominal cavity was performed at the discretion of the operating surgeon, refusal from routine drainage was preferable (in the absence of technical difficulties during the operation and doubts about satisfactory hemostasis);

— in the postoperative period, an early start of enteral nutrition was carried out (liquid food was taken 3 hours after the operation, solid food was taken on the next day). In the postoperative period, there were no complications associated with the early onset of enteral nutrition, in particular episodes of nausea and vomiting. Peristalsis was satisfactory in all patients during the first days after surgery.

— anesthesia was strictly regulated, multimodal and was carried out according to the scheme with the use of drugs of 2 groups: Sol. tramadoli 5% 2.0 intramuscularly 6 hours after surgery; Sol. ketoroli 2.0 intramuscularly 4 times a day for the first 3 days, then orally until discharge.

— we carried out early mobilization after surgery - after 6 hours, patients were activated.

Drugs used for postoperative pain relief (INN - International Nonproprietary Name):

Tramadol – manufacturer (all stages, including quality control), Open Joint Stock Company "Organic" (JSC "Organic"), Russia, 654034, Kemerovo Region, Novokuznetsk, Kuznetsk highway, 3.

Ketorolac – manufacturer (all stages, including quality control), Open Joint Stock Company Kurgan Joint Stock Company of Medicines and Products Sintez (OJSC Sintez), Russia, 640008, Kurgan Region, Kurgan, Constitution Avenue, 7.

GENOTYPING CYP2D6

Patients underwent pharmacogenetic testing for CYP2C9 (allelic variants CYP2C9*2, CYP2C9*3), CYP2D6 (allelic variants CYP2D6* 4) by real-time PCR (Bio Rad CFX96). The selection of the candidate gene and polymorphism (SNP) was carried out using the service PharmGKB (https://www.pharmgkb.org) — combinatorial / haplotype analysis was performed.

Pharmacogenetic testing was carried out at the Research Institute of Molecular and Personalized Medicine of RMANPO. During the study, the following equipment was used: DNA amplifier for real-time PCR Bio Rad CFX96. Genotyping using real-time PCR; PCR boxes for sterile work Lamsystems « Laminar-S»; low temperature freezers Sanyo; sets of automatic dispensers Vortex Biosan V-1 plus; vortex centrifuge; microspin Biosan FV-2400; vortex centrifuge Biosan MultiSpin; centrifuge MiniSpin Eppendorf; analytical weighing scales Adventure Pro Ohaus; weighing scales Scout Pro Ohaus.

STATISTICAL ANALYSIS

Statistical processing of the results was carried out by software STATISTICA 10. Using the Shapiro-Wilk test, the data were checked for normality. Given that the data did not meet the criteria for normality, statistical comparisons between the two independent groups were performed using the Mann-Whitney U-test. Statistical significance was set at 0.05. Data are presented as mean ± standard deviation.

RESULTS

Table 1 shows the demographic distribution and intraoperative parameters of patients.

GENOTYPE DISTRIBUTION FOR CYP2D6 AND CYP2C9

In general, all patients for polymorphic CYP2D6*4 were homozygous for wild-type in 78.5%; homozygotes and heterozygotes for the mutant allele in 21.5%. According to the polymorphic marker CYP2C9*2, wild-type homozygotes (not carriers of the mutant gene) were found in 79.4%; homozygotes and heterozygotes for the mutant allele – in 20.6%. For the polymorphic marker CYP2D6*3, wild-type homozygotes were found in 82.2%; homozygotes and heterozygotes for the mutant allele in 17.8%. The distribution of genotypes is presented in Table. 2.

RESULTS OF DATA VAS THE MAC-GILL PAIN SCALE

EFFECT OF CYP2D6*4 ON THE EFFECTIVENESS OF ANALYSIS WITH TRAMADOL

When comparing the intensity of postoperative pain depending on the presence or absence of the polymorphic marker CYP2D6*4, the following results were obtained (Table. 3). Carriers of the CYP2D6*4 polymorphism had a higher number of points according to the VAS data in all studied time intervals (time interval in Table 3), as well as according to the McGill pain questionnaire, while after 24 hours statistically significant differences according to the VAS were noted. Since the postoperative administration of tramadol was 6 hours after the operation, the results obtained may be of considerable interest.

INFLUENCE OF CYP2C9*2 AND CYP2C9*3 ON THE EFFECTIVENESS OF ANALYSIS WITH KETOROLAC

When comparing the intensity of postoperative pain syndrome depending on the presence or absence of polymorphic markers CYP2C9*2 and CYP1C9*3, the following results were obtained: in homozygotes and heterozygotes for the mutant allele CYP2C9*2, the intensity of pain syndrome (according to VAS data) was lower in all studied time intervals, while after 12, 24, 36 and 48 hours, statistically significant differences were obtained. According to the McGill pain rating scale, there is also a decrease in the intensity of postoperative pain by more than one point in carriers of the polymorphic marker CYP2C9*2 (Table 4); homozygotes and heterozygotes for the mutant allele CYP2C9*3 have a lower number of points after 2 and 6 hours, as well as according to the McGill pain rating scale, while according to the McGill scale the difference is more than 4 points (Table 5).

DISCUSSION

Our study was aimed at determining the role of the influence of polymorphisms of the CYP2D6 and CYP2C9 genes on the clinical efficacy of tramadol and ketorolac, respectively, in postoperative pain relief. In the foreign literature, there are many works on the effect of CYP2D6 on opioid metabolism. In particular, CYP2D6 is involved in the conversion of codeine and tramadol into their active metabolites - morphine and oxy-desmethyltramadol, respectively; in addition, oxycodone is metabolized by CYP2D6 to oxymorphone, and hydrocodone into hydromorphone. The effectiveness and safety of the listed drugs is determined by the activity of CYP2D6 [17]. Depending on the activity of CYP2D6, the following types of metabolizers are phenotypically distinguished: slow, intermediate, fast and ultrafast [18–19]. In the presence of slow metabolizers, the effectiveness of analgesic therapy is low [18–19]. In contrast, ultrafast metabolizers, due to the rapid conversion of opioids to active metabolites, lead to a high risk of toxicity [17, 19]. Studies on the use of codeine and tramadol show that children with the ultrafast metabolizer phenotype have an increased risk of respiratory depression [20] and increased mortality [21] from taking these drugs. Also, the effectiveness of pharmacogenetics with the use of tramadol has been described in a number of studies [22–24]. In our study, in patients homozygous and heterozygous for the CYP2D6*4 mutant allele, a slow metabolizer of tramadol, the effectiveness of pain relief was lower than in wild-type patients (Table 2). 3).

Most of the work on assessing the role of the influence of the CYP2C9 gene polymorphism on the use of NSAIDs is aimed at studying the pharmacokinetics and adverse reactions from NSAIDs, in particular for GIB, but not assessing the clinical efficacy of pain relief [12, 16, 25, 26]. In a study evaluating the role of the influence of CYP2C8 and CYP2C9 gene polymorphisms on the effectiveness of pain relief and adverse reactions from taking celecoxib after adenotonsilectomy in children, the authors concluded that, in general, there is no correlation between the frequency of adverse reactions and the genotype, however, insignificant differences in clinical effectiveness were obtained; in particular, the authors report that the CYP2C9*3 allele provides improved analgesic efficacy of celecoxib and functional recovery without increasing adverse reactions [27]. In a 2017 study to determine the relationship of CYP2C8*3 and CYP2C9 with the clinical efficacy of piroxicam for postoperative pain and inflammatory symptoms, the authors found no correlation between carriers of mutant alleles and wild-type carriers. [28]. Similarly, V. Rollason et al., in their study, did not find a connection between the genotype and the effectiveness of pain relief and adverse reactions from NSAIDs. [29]. However, in our study, it was found that in carriers of CYP2C9*2, the effectiveness of pain relief from taking ketorolac was statistically significantly higher after 12, 24, 36 and 48 hours according to the VAS and McGill data (Table 4), and in carriers of CYP2C9*3, pain relief was more effective only after 2.6 hours according to VAS and according to McGill, but these results are not statistically significant (Tabl. 5).

CONCLUSION

In our study, the carriers of the CYP2D6*4 genotype had a more intense pain syndrome than the wild type, and the effectiveness of pain relief, respectively, was lower. In carriers of CYP2C9*2, the effectiveness of pain relief was higher than in the wild type, and the pain syndrome was lower. In carriers of CYP2C9*3, the score was lower only after 2.6 hours and according to the McGill scale. The effect of genetic variants on drug response for NSAIDs and tramadol has been described in many studies. The data are diverse, but in most studies, the authors note a significant relationship between the genotype and the effectiveness and safety of drugs. Therefore, it is necessary to conduct more large-scale studies with analgesic drugs used in the postoperative period in patients after video laparoscopic and traditional operations, since these groups of drugs represent different variations in relation to the genetic influence of enzymes of the family CYP. The use of a pharmacogenetic approach can make it possible to rationalize the prescription of painkillers, increasing their effectiveness and reducing the risk of developing adverse reactions, which in turn can increase the effectiveness of the concept of accelerated recovery.

FINDINGS

1. The presence of the polymorphic marker CYP2D6*4 may reduce the effectiveness of postoperative tramadol analgesia compared with wild type.

2. The presence of the polymorphic marker CYP2C9*2 and CYP2C9*3 may increase the effectiveness of ketorolac pain relief compared to wild type.

REFERENCES

1. Kehlet H. The stress response to anaesthesia and surgery: release mechanisms and and modifying factors. *Clin Anaesthesiol*. 1984;2:315–339.
2. Frazee R, Abernathy S, Davis M, Isbell T, Regner J, Smith R. Fast track pathway for perforated appendicitis. *Am J Surg*. 2017;213(4):739–741. PMID: 27816201 https://doi.org/10.1016/j.amjsurg.2016.08.006
3. Wu C, Raja S. Treatment of acute postoperative pain. *Lancet*. 2011;377(9784):2215–2225: PMID: 21704871 https://doi.org/10.1016/S0140-6736(11)60245-6
4. Kukes VG, Sychev DA, Ramenskaya GV, Ignat'ev IV. Farmakogenetika sistemy biotransformatsii i transporterov lekarstvennykh sredstv: ot teorii k praktike. *Journal Biomed*. 2007;(6):29–47. (In Russ.)
5. Evans WE, McLeod HL. Pharmacogenomics — Drug Disposition, Drug Targets, and Side Effects. *N Engl J Med.* 2003;348(6):538-549: PMID: 12571262 https://doi.org/10.1056/NEJMra020526
6. Crews K, Hicks J, Pui C, Relling MV, Evans WE. Pharmacogenomics and Individualized Medicine: Translating Science Into Practice. *Clin Pharmacol Ther*. 2012;92(4):467–475: PMID: 22948889 https://doi.org/10.1038/clpt.2012.120
7. Grachev SV, Sychev DA, Ramenskaya GV. *Metabolizm lekarstvennykh sredstv. Nauchnye osnovy personalizirovannoy meditsiny*. Moscow: GEOTAR-Media Publ.; 2008. (In Russ.)
8. Mercadante S. Opioid metabolism and clinical aspects. *Eur J Pharmacol*. 2015;769:71–78: PMID: 26522929 https://doi.org/10.1016/j.ejphar.2015.10.049
9. Stamer U, Musshoff F, Kobilay M, Madea B, Hoeft A, Stuber F. Concentrations of tramadol and O-desmethyltramadol enantiomers in different CYP2D6 genotypes. *Clin Pharmacol Ther*. 2007;82(1):41–47: PMID: 17361124 https://doi.org/10.1038/sj.clpt.6100152
10. Yang Z, Arheart K, Morris R, Morris R, Zhang Y, Rodriguez Y, et al. CYP2D6 poor metabolizer genotype and smoking predict severe postoperative pain in female patients on arrival to the recovery room. *Pain Med*. 2012;13(4):604–609: PMID: 22497725 https://doi.org/10.1111/j.1526-4637.2012.01296.x
11. Slanar O, Dupal P, Matouskova O, Vondrackova H, Pafko P, Perlik F. Tramadol efficacy in patients with postoperative pain in relation to CYP2D6 and MDR1 polymorphisms. *Bratislava Med J*. 2012;113(3):152–155: PMID: 22428763 https://doi.org/10.4149/bll_2012_036
12. Krasniqi V, Dimovski A, Domjanović I, Bilić I, Božina N. How polymorphisms of the cytochrome P450 genes affect ibuprofen and diclofenac metabolism and toxicity. *Arh Hig Rada Toksikol*. 2016;67(1):1–8: PMID: 27092633 https://doi.org/10.1515/aiht-2016-67-2754
13. Llerena A, Alvarez M, Dorado P, González I, Peñas-LLedó E, Pérez B, et al. Interethnic differences in the relevance of CYP2C9 genotype and environmental factors for diclofenac metabolism in Hispanics from Cuba and Spain. *Pharmacogenomics J*. 2013;14(3):229–234: PMID: 23959274 https://doi.org/10.1038/tpj.2013.28
14. Lee C., Pieper J.A, Frye R, Hinderliter AL, Blaisdell JA, Goldstein JA. Differences in flurbiprofen pharmacokinetics between CYP2C9*1/*1, *1/*2, and *1/*3 genotypes. *Eur J Clin Pharmacol Pharmacokinet Dispos*. 2003;1(58):791–794: PMID: 12698304 https://doi.org/10.1007/s00228-003-0574-6
15. Zhang Y, Zhong D, Si D, Guo Y, Chen X, Zhou H. Lornoxicam pharmacokinetics in relation to cytochrome P450 2C9 genotype. *Br J Clin Pharmacol*. 2005;59(1):14–17: PMID: 15229460 https://doi.org/10.1016/j.clpt.2004.03.002
16. Vianna-Jorge R, Perini J, Rondinelli E, Suarez-Kurtz G. CYP2C9 genotypes and the pharmacokinetics of tenoxicam in Brazilians*1. *Clin Pharmacol Ther*. 2004;76(1):18–26: PMID: 15229460 https://doi.org/10.1016/j.clpt.2004.03.002
17. Crews K, Gaedigk A, Dunnenberger H, Leeder JS, Klein TE, Caudle KE, et al. Clinical Pharmacogenetics Implementation Consortium Guidelines for Cytochrome P450 2D6 Genotype and Codeine Therapy: 2014 Update. *Clin Pharmacol Ther*. 2014;95(4):376–382: PMID: 24458010 https://doi.org/10.1038/clpt.2013.254
18. Balyan R, Mecoli M, Venkatasubramanian R, Chidambaran V, Kamos N, Clay S, et al. CYP2D6 pharmacogenetic and oxycodone pharmacokinetic association study in pediatric surgical patients. *Pharmacogenomics*. 2017;18(4):337–348: PMID: 28244808 https://doi.org/10.2217/pgs-2016-0183
19. Owusu Obeng A, Hamadeh I, Smith M. Review of Opioid Pharmacogenetics and Considerations for Pain Management. *Pharmacotherapy*. 2017;37(9):1105–1121: PMID: 28699646 https://doi.org/10.1002/phar.1986
20. Orliaguet G, Hamza J, Couloigner V, Denoyelle F, Loriot M-A, Broly F, et al. A Case of Respiratory Depression in a Child With Ultrarapid CYP2D6 Metabolism After Tramadol. *Pediatrics*. 2015;135(3):753–755: PMID: 25647677 https://doi.org/10.1542/peds.2014-2673
21. Kelly L, Rieder M, van den Anker J, Malkin B, Ross C, Neely MN, et al. More Codeine Fatalities After Tonsillectomy in North American Children. *Pediatrics*. 2012;129(5):1343–1347: PMID: 22492761 https://doi.org/10.1542/peds.2011-2538
22. Sokolov DA, Lyuboshevskiy PA, Ganert AN. Influence of Cytochrome P-450 Genetic Polymorphisms on the Main and Side Effects of Tramadol in the Postoperative Period. *Regional Anesthesia and Acute Pain Management*. 2017;11(4):240–246. https://doi.org/10.18821/1993-6508-2017-11-4-240-246 (In Russ.)
23. Dong H, Lu S, Zhang R, Liu D-D, Zhang Y-Z, Song C-Y. Effect of the CYP2D6 gene polymorphism on postoperative analgesia of tramadol in Han nationality nephrectomy patients. *Eur J Clin Pharmacol*. 2015;(246):681–686: PMID: 25948472 https://doi.org/10.1007/s00228-015-1857-4
24. Wang G, Zhang H, He F, Fang XM. Effect of the CYP2D6*10 C188T polymorphism on postoperative tramadol analgesia in a Chinese population. *Eur J Clin Pharmacol*. 2006;62(11):927–931: PMID: 16960721 https://doi.org/10.1007/s00228-006-0191-2
25. Martínez C, Blanco G, Ladero J, García-Martín E, Taxonera C, Gamito FG, et al. Genetic predisposition to acute gastrointestinal bleeding after NSAIDs use. *Br J Pharmacol*. 2004;141(2):205–208: PMID: 14707031 https://doi.org/10.1038/sj.bjp.0705623
26. Agúndez J, García-Martín E, Martínez C. Genetically based impairment in CYP2C8- and CYP2C9-dependent NSAID metabolism as a risk factor for gastrointestinal bleeding: Is a combination of pharmacogenomics and metabolomics required to improve personalized medicine? *Expert Opin Drug Metab Toxicol*. 2009;5(6):607–620: PMID: 19422321 https://doi.org/10.1517/17425250902970998
27. Murto K, Lamontagne C, McFaul C, MacCormick J, Ramakko K-A, Aglipay M, et al. Celecoxib pharmacogenetics and pediatric adenotonsillectomy: a double-blinded randomized controlled study. *Can J Anaesth*. 2015;62(7):785–797: PMID: 25846344 https://doi.org/10.1007/s12630-015-0376-1
28. Calvo A, Zupelari-Gonçalves P, Dionísio T, Brozoski DT, Faria FA, Santos CF. Efficacy of piroxicam for postoperative pain after lower third molar surgery associated with CYP2C8*3 and CYP2C9. *J Pain Res*. 2017;10:1581–1589: PMID: 28740425 https://doi.org/10.2147/JPR.S138147
29. Rollason V, Samer CF, Daali Y, Desmeules JA. Prediction by Pharmacogenetics of Safety and Efficacy of Non-Steroidal Anti- Inflammatory Drugs: A Review. *Curr Drug Metab*. 2014;15(3):326–343: PMID: 24524667 https://doi.org/10.2174/1389200215666140202214 45

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