Review Article

Gene polymorphism impact on opioid analgesic usage

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J. Adv. Pharm. Technol. Res.

Abstract

Acute pain, moderate-to-severe cancer pain, and persistent malignant pain are all frequently treated with opioids. It is regarded as one of the main tenets of analgesic treatment. The relationship between human opioid sensitivity and genetic polymorphism differences has received little attention up to this point in research. Nonetheless, there is mounting proof that pharmacogenomic diversity could affect how each person reacts to opioids. Finding out how gene polymorphism affects analgesic use is the aim of this investigation, particularly opioids. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses standards were followed in the preparation of the systematic review approach used in this work. Oxycodone, fentanyl, raclopride, tramadol, ketorolac, morphine, ropivacaine, levobupivacaine, subfentanyl, remifentanil, and nortriptyline were the opioid medications used in the study, which was based on 13 publications. From those articles, we reviewed the impact of gene polymorphism on pain management and drug pharmacokinetics. Based on this systematic review, we concluded that gene polymorphism of gene affects analgesic, specifically opioid mechanisms.

Key words: Impact, opioid, polymorphism, usage

INTRODUCTION

Opioids are crucial for managing acute, moderate-to-severe cancer pain and chronic malignant pain.[1,2] However, clinical effectiveness can vary due to factors such as individual opioid responsiveness, improper dosage, and adverse reactions. Genetic differences can directly affect opioid pharmacokinetics and pharmacodynamics, highlighting the need for further research into genes related to opioid receptors, metabolic enzymes, and drug transporters.[3,4]

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Submitted: 19-Feb-2024 **Revised:** 02-Jun-2024
Accepted: 10-Jun-2024 **Published:** 22-Jul-2024

Access this article online	
Quick Response Code:	Website: https://journals.lww.com/JAPTR
	DOI: 10.4103/JAPTR.JAPTR_69_24

Cytochrome P450 (CYP) enzymes, particularly CYP2D6 and CYP3A4, are crucial for metabolizing opioids, neuroleptics, and antidepressants. Genetic variations in CYP2D6, with around 80 allelic variations, impact the effectiveness of specific medications such as tramadol, dihydrocodeine, and codeine.[5-7]

Pharmacogenetic investigations have focused on genes such as MDR-1, COMT, and the mu-opioid receptor (OPRM).[8,9] The μ-opioid receptor primarily mediates opioid effects, and genetic variations can influence opioid dosage requirements and analgesic efficacy.[10-12] Variations in the COMT gene, such as the Val158Met variant,[13-15] influence the effectiveness of morphine in pain management.[16]

This study is to understanding the influence of gene polymorphisms on analgesic utilization, particularly with opioids.

How to cite this article: Widjaja SS, Ichwan M, Chowbay B, Rusdiana, Mardani TH, Jayalie VF. Gene polymorphism impact on opioid analgesic usage. J Adv Pharm Technol Res 2024;15:135-8.

METHODS

This study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The systematic review process followed the PICO framework: (1) Population: Humans receiving opioids; (2) Intervention: Gene polymorphism; (3) Comparison: Individuals without gene polymorphism; and (4) Outcome: Pain Scale (e.g. Visual Analog Scale) and pharmacokinetic parameters (e.g., T1/2, area under the curve). Articles were searched in PubMed, Science Direct, Scopus, and Cochrane using Boolean Operators ("OR," "AND," "NOT") and keywords such as "Polymorphism," "Opioid receptor," "Analgesics," and "Genomics." Inclusion criteria included original English articles with full text, focusing on the impact of gene polymorphism on opioid usage. Data extracted from each article included the researcher name, year of publication, study design, opioid used, and study results.

RESULTS

Initially, 1919 articles were identified: 235 from PubMed, 344 from Scopus, 1,320 from Science Direct, and 20 from Cochrane. First, 457 duplicate articles were removed. Next, titles and abstracts were screened, excluding 743 articles and 512 non-English articles. In the third screening, 34 articles could not be retrieved, the final screening excluded 107 articles for unsuitable Patient, Population or Problem; Intervention; Comparison; Outcome (PICO), 32 for incompatible outcomes, and 21 for incomplete data. Consequently, 13 articles were selected for further study.

The review included 13 articles that investigated various opioids: oxycodone,[17-21] fentanyl,[22-25] raclopride,[23] tramadol,[22,26,27] ketorolac,[22] morphine,[28,29] ropivacaine,[22] levobupivacaine,[22] subfentanyl,[22] remifentanil,[24]and nortriptyline.[29] Several studies reported an association between gene polymorphisms and analgesic effects.[18,19,22,23,28] Samer *et al*. found that CYP2D6 genetic polymorphism affects opioid pharmacodynamics.[18] De Capraris *et al*. noted that the OPRM1 118A>G polymorphism influences postoperative pain response in heterozygous patients, potentially affecting analgesic efficacy.[22] However, some studies showed that gene polymorphism does not have an association with analgesic effects.[20,24,26,29]

Saiz-Rodríguez *et al*. observed that CYP2D6 intermediate metabolizers (IM) exhibited elevated tramadol plasma levels and reduced clearance in contrast to normal and ultrarapid metabolizers (UM).[27] However, Saiz-Rodríguez *et al*. reported that CYP3A5*3, ABCB1 C3435T, and ABCB1 G2677T/A were not correlated with the pharmacokinetics, pharmacodynamics, and safety aspects of fentanyl.[25]

DISCUSSION

The internal opioid system, consisting of mu (μ), delta (δ), and kappa (κ) receptors, influences motivation, reward, well-being, and addiction, which is driven by the μ-opioid receptor system.[30]

Genetic polymorphisms in OPRM1, such as A118G, significantly affect the efficacy of methadone.[31,32] A118G variant can alter the mu-opioid receptor's structure and function, impacting opioid responsiveness.[33] *In silico* studies show that individuals with the G118 variant have a three-fold higher affinity for endogenous opioids compared to exogenous ones.[34] The A118G polymorphism may also have allele-specific effects on the plasma cortisol response to opioid blockade (e.g., naltrexone) at OPRM1 receptors.[30]

Studies indicate that individuals with the homozygous version (GG) of the A118G polymorphism have reduced morphine efficacy, requiring larger opioid dosages to achieve therapeutic effects.[30] Research by Ho *et al*. (2019) suggests that the minor allele (G) of the OPRM1 A118G polymorphism is associated with an increase in pressure pain threshold following morphine administration,[35] while some studies suggest increased opioid consumption with this variant, others indicate a decrease, with some showing no discernible difference.[30]

Variations in genetic polymorphisms in genes encoding cytochrome P450 isoenzymes lead to differing responses to maintenance therapies, affecting the required dosage for treatment.[30]

Individuals with the CYP2B6 G516T T/T genotype showed higher tramadol plasma levels, with no other genetic variations affecting tramadol pharmacokinetics.[36,37] The CYP2B6 genotype notably correlates with increased tramadol concentrations due to its impact on tramadol clearance. Conversely, Saiz-Rodríguez *et al*. (2019) found no evidence linking CYP3A5*3, ABCB1 C3435T, and ABCB1 G2677T/A to fentanyl's pharmacokinetics, pharmacodynamics, or safety profile.[25]

Moreover, individuals with the CYP3A4*22 genotype had higher fentanyl AUC and lower clearance. Since fentanyl is mainly metabolized by CYP3A4, this variant significantly impacts its metabolism.[25,38]

Tramadol primarily metabolizes through CYP2D6 to M1. The CYP2D6 poor metabolizer (PM) phenotype is linked to reduced M1 formation,[39,40] but some studies found no significant correlation.[41] Individuals with lower CYP2D6 activity may need higher tramadol dosages and might respond poorly to other opioids such as codeine or oxycodone.[38,42-44] Limited data on CYP2D6 UM showed no notable differences in tramadol's analgesic effects compared

to extensive/normal metabolizers (NM).[44,45] CYP2D6 IM–PM are associated with a lower risk of adverse reactions, while UM phenotypes carry a higher risk of toxicity. Despite ongoing debate, the Dutch pharmacokinetics working group suggests higher doses or alternative treatments for PM and IM patients and a 40% dose reduction for UM individuals due to increased toxicity risk.[27,44-46] However, tramadol is also metabolized into M2 by the CYP3A4/CYP2B6 isoenzyme.[47]

The CYP3A4*22 reduced function allele affects the pharmacokinetics of several drugs.[48-50] One study found no significant effect of the G516T loss of function polymorphism on tramadol clearance in neuropathic pain.[51] Another study reported lower M2 AUC and higher tramadol AUC in individuals with reduced function alleles of CYP2B6 and CYP2D6 NM.[52] Patients with the SLC22A1 "nonactive allele" phenotype were expected to have higher M1 but lower tramadol concentrations.[53]

This study has limitations, including a lack of large sample sizes. Therefore, more extensive research on the impact of gene polymorphisms on opioid analgesic use is necessary.

CONCLUSION

This systematic review indicates that gene polymorphisms affect the analgesic effects of opioids, particularly their pharmacokinetics, influencing AUC and clearance values. Gene polymorphism testing could, therefore, be useful in optimizing opioid use. However, conflicting results highlight the need for further research on this topic.

Acknowledgment
This study was supported by the Ministry of Research and Technology and Higher Education Republic, Indonesia, under the research grant TALENTA.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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