Pharmacogenomics of analgesics in anesthesia practice: A current update of literature

Keith Gray, Sanjib D. Adhikary, Piotr Janicki
Department of Anesthesiology and Perioperative Medicine, Penn State College of Medicine, Hershey, Pennsylvania, USA

Abstract

The field of pharmacogenomics seeks to understand how an individual’s unique gene sequence can affect their response to certain drugs. It is particularly relevant in anesthesia when the interindividual response to pain medication is essential. Codeine and tramadol are prodrugs metabolized by CYP2D6, polymorphisms of which can cause dangerous or even fatal levels of their metabolites, or decrease the level of metabolites to decrease their analgesic effect. Many other opioids are metabolized by CYP2D6 or CYP3A4, of which loss-of-function variants can cause dangerous levels of these drugs. The OCT1 transporter facilitates the movement of drugs into hepatocytes for metabolism, and variants of this transporter can increase serum levels of morphine and O-desmethyltramadol. Many NSAIDs are metabolized by CYP2C9, and there is concern that variants of this enzyme may lead to high serum levels of these drugs, causing gastrointestinal bleeding, however the data does not strongly support this. The ABCB1 gene encodes for P-glycoprotein which facilitates efflux of opioids away from their target receptors. The C3435T SNP may increase the concentration of opioids at target receptors, although the data is not conclusive. Catechol-O-Methyltransferase (COMT) is shown to indirectly upregulate opioid receptors. Certain haplotypes of COMT have been demonstrated to have an effect on opioid requirements. The OPRM1 gene codes for the mu-opioid receptor, and there is conflicting data regarding its effect on analgesia and opioid requirements. Overall, there is a fair amount of conflicting data in the above topics, suggesting that there is still a lot of research to be done on these topics, and that pain perception is multifactorial, likely including many common genetic variants.

Keywords: Analgesic, pharmacogenomics, polymorphism

Introduction

A daily challenge that faces the clinical anesthesiologist is the great variability of the response of a given patient to a specific dose of a certain medication, and in particular, analgesic drugs. While this extraordinary variability in patient response to pharmacotherapy is certainly multifactorial, much research has been done in the use of molecular medicine to generate predictions regarding clinical response to medication based on the patient’s personal DNA signature. This field of study has been termed “pharmacogenomics,” and has pursuits in both pharmacokinetics and pharmacodynamics, with the goal of creating “personalized medicine” in which medical treatment is customized according to an individual’s genetic signature.¹

Methods

This review included the relevant current literature regarding pharmacogenomics as pertaining to the use of analgesics in anesthesia practice. A systematic search of PubMed, Google Scholar, and Cochrane Database was done in May 2016 using the key words Pharmacogenomics, Anesthesia, CYP polymorphism, and metabolizers. The...
search retrieved 165 titles and abstracts, hence, the search was restricted to only human studies published in English. Letters, commentaries, editorials, and case reports were not included to be part of selected materials to be reviewed. Total of 84 articles were reviewed. All literature related to CYP polymorphism and analgesics were included. However, no formal criteria except those mentioned above were applied for inclusion or exclusion of studies.

The differences in the genotypes associated with CYP polymorphism produce several types of distinct clinical pain phenotypes presented in Table 1.

### Pharmacokinetics – prodrug activation

**Codeine:** Codeine is a prodrug, which is demethylated by the CYP2D6 enzyme (a subtype of cytochrome P450) to morphine, which has 200 times the affinity for the mu-opioid receptor compared to codeine. The CYP2D6 enzyme is highly polymorphic, with over 100 alleles identified thus far. Some of these alleles can lead to inactivation, reduction in function, or duplication of the enzyme. These various genotypes have been described with their accompanying phenotypes. Two nonfunctioning alleles are associated with poor metabolism, one or two functioning alleles are associated with extensive metabolism, and duplicated alleles or an allele with a promoter function are associated with ultrarapid metabolism. The ultra-metabolizers tend to produce more active metabolites from codeine (e.g., morphine, morphine-6-glucuronides) which are more active on opioid receptor than the codeine substrate which acts in this case as prodrug. As a result, opioid side effects (e.g., respiratory depression) observed in ultra-metabolizers might be much more pronounced that extensive (normal) metabolizers.

One early case report showed life-threatening opioid intoxication from codeine prescribed for cough in a patient with bilateral pneumonia who was later found to have three functioning CYP2D6 alleles, consistent with ultrarapid metabolism. Subsequent case reports described apnea in a child following oral codeine administration, later found to have CYP2D6 allele with a promoter function, and death in a child following codeine administration following adenotonsillectomy, who was found to have supertherapeutic levels of codeine and functional duplication of CYP2D6. Of note, as with many children undergoing adenotonsillectomy, the child had obstructive sleep apnea, which already increases the risk of hypoxemia. A follow-up case report described several more fatal or life-threatening incidents in children taking codeine following adenotonsillectomy. One case report also revealed apnea leading to death in a nursing newborn of a mother taking codeine, who was found to have a genotype associated with ultrarapid metabolism, and a case-control study demonstrated severe respiratory depression in breastfeeding newborns with mothers having an ultrarapid metabolism genotype. Due to this mounting evidence, the Food and Drug Administration issued a Black Box Warning for codeine in May, 2013, listing it as contraindicated in pediatrics following adenoidectomy and/or tonsillectomy, and adding a warning regarding breastfeeding mothers taking codeine. This also led the Clinical Pharmacogenetics Implementation Consortium to publish guidelines regarding the use of genotyping and the prescription of codeine.

In addition, one observational study evaluated the effectiveness of codeine in postpartum analgesia following elective caesarean section, and found that patients with genotypes associated with poor metabolism received no analgesia from codeine, whereas those with genotypes associated with ultrarapid metabolism experienced sedation.

**Tramadol:** Similar to codeine, tramadol is also a prodrug metabolized by CYP2D6, which converts it to its active metabolite, O-desmethyltramadol, also referred to as (+)-M1, which has mu-opioid activity. Experimental pain studies found that patients with genotypes associated with ultrarapid metabolism experienced reduced discomfort from experimental pain, accompanied by increased serum levels of the tramadol metabolite, whereas patients with genotypes associated with poor metabolism had little clinical effect with minimally detectable tramadol metabolite. In similar fashion to codeine, there are case reports that describe respiratory depression in patients taking tramadol that are later found to have an ultrarapid metabolizing genotype, both in a patient with renal impairment and in a child after adenotonsillectomy.

### Table 1: Relationship between genotypes and phenotypes for CYP activity in opioid metabolizing pathways

| Clinical Opioid Dosage | Laboratory Terminology | Genomic correlation |
|------------------------|------------------------|---------------------|
| Normal                 | Extensive (normal) metabolizers | Wild-type homozygote or carrier of recessive variant |
|                       | EM or NM                |                     |
| Significantly increased| Rapid (or ultrarapid) metabolizers | Carriers of more than two copies of alleles (copy number variants) |
|                       | UM                      |                     |
| Somewhat increased     | Intermediate metabolizer | Two copies of decreased functional recessive allele or carrier of dominant dysfunctional allele |
|                       | IM                      |                     |
| Decreased dose because not metabolizing opioids, e.g., causing toxicity | Poor metabolizer | Two copies of recessive alleles or heterozygous carriers of dominant nonfunctional allele |
|                       | PM                      |                     |
The results of clinical trials vary as patients with a poor metabolizing genotype receiving tramadol following abdominal surgery required more additional/rescue opioids than patients with an extensive metabolizing genotype,[18] whereas patients with a poor metabolizing genotype receiving tramadol following knee arthroscopy attested to better analgesia than patients with an extensive metabolizing genotype.[19] This suggests that during intense pain the therapeutic effects of tramadol may rely more heavily on its opioid metabolite, but during less-severe pain the nonopioid effects of tramadol itself may be more beneficial.

**Pharmacokinetics – elimination**

Opioids: Many opioids aside from codeine are also metabolized by cytochrome P450 enzymes for elimination, and thus, have been studied through the lens of pharmacogenomics. Although alfentanil is known to be metabolized by CYP3A5, study on multiple allele variants failed to show differences in systemic clearance.[20] Fentanyl is also known to be metabolized by CYP3A5, and a study in cancer patients transitioning to transdermal fentanyl revealed that those who were homogenous for the decreased function CYP3A5*3 variant had increased fentanyl plasma concentrations and an increased rate of central nervous system side effects.[21] The CYP3A4 enzyme has also been shown to play a role in the elimination of fentanyl, with patients possessing the CYP3A4*1 allele having a significantly lower postoperative fentanyl requirement.[22] Hydrocodone is known to be metabolized by the CYP2D6 enzyme, and a case report documented a case of fatal hydrocodone overdose in a child who was later found to have a genotype associated with poor metabolism.[23] Morphine in also a metabolized by CYP2D6, although its alleles appear to have a counterintuitive effect in a study where patients with a genotype associated with ultrarapid metabolism had decreased morphine requirements after elective surgery.[24]

The organic cation transporter 1 (OCT1) facilitates the uptake of drugs into hepatocytes for metabolism. The serum levels of morphine and O-desmethyltramadol (tramadolactive metabolite) are influenced by variations in OCT1.[25,26] Of note, the activation of tramadol and codeine take place independently of OCT1, and thus, the accumulation of the metabolites can still occur based on variations in the transporter. Clinical studies on serum morphine levels in pediatric patients following adenotonsillectomy showed reduced morphine clearance in patients with loss-of-function OCT1 variants.[27,28]

NSAIDs: Nonsteroidal anti-inflammatory drugs such as naproxen and celecoxib have been studied from a pharmacogenomic standpoint primarily regarding their side-effect profile, specifically gastrointestinal (GI) bleeding. As with the medications already discussed, many NSAIDs are metabolized by cytochrome P450 enzymes, specifically CYP2C8 and CYP2C9. The CYP2C9 polymorphisms were initially studied, and the loss-of-function allele CYP2C9*3, when homozygous, was associated with a two-fold reduction in celecoxib clearance compared to the wild type.[29] A later study failed to demonstrate any difference in plasma levels of naproxen in heterozygous patients of the CYP2C9*3 allele.[30] Studies regarding gastrointestinal bleeding have mixed results, with a few studies showing the CYP2C9*3 allele to be associated with a significantly higher risk of bleeding.[31,32]while other studies failed to show a difference in the risk of GI bleeding,[33,34] although one study showed a significant difference in risk in patients with a specific combined CYP2C8 and CYP2C9 mutation.[35] It should be noted that these mutations are quite rare, thus making it difficult for studies to achieve significant power.

**Pharmacokinetics – Transmembrane transport**

The ABCB1 gene encodes for P-glycoprotein (PGP) which facilitates the access of xenobiotics to the brain and causes efflux of opioids away from their target receptors. A specific single nucleotide polymorphism (SNP) of the gene which encodes PGP has been found to modulate its activity. This SNP, labelled C3435T, has been shown to improve the efficacy of opioids in experimental pain.[36] This same SNP has also been shown to decrease postoperative pain in pediatrics[37] and to decrease opioid requirements for postoperative pain[38] and cancer pain.[21,39,40] Thus, the C3435T SNP likely decreases PGP activity, which reduces efflux of opioids away from target receptors, thus increasing concentration at opioid receptors. This is consistent with a study that found C3435T to be associated with opioid-induced respiratory depression,[41] and case reports that linked it to respiratory depression in pediatric patients following adenotonsillectomy.[42,43] However, there are some studies that failed to show a relationship between ABCB1 variations and postoperative pediatric pain scores,[44] analgesic effect of oxycodone on postoperative (PO) pain,[45] or morphine use in patients following caesarean section.[46]

**Pharmacodynamics – COMT**

COMT degrades catecholamines. A variant of COMT (val158met), where a valine is substituted by methionine at codon 158 is produced by SNP G772A has reduced activity which increases dopamine levels. This increased level of circulating dopamine suppresses endogenous opioid production, which in turn upregulates opioid receptors. This increase in opioid binding sites in response to this variant has been seen in postmortem brain cells,[47] and val158met has been shown to decrease regional/endogenous mu-opioid system response and cause higher pain ratings to experimental pain.[48]
An early study demonstrated val158met heterozygosity as being linked to decreased opioid requirements for cancer pain. These findings were later reproduced for postoperative pain. However, many more studies failed to show significance of the val158met variant as produced by the SNP G772A, and instead showed significance in certain COMT haplotypes, which are a set of polymorphisms that have a tendency toward being inherited together. These haplotypes were found to modulate COMT activity, experimental pain sensitivity, and opioid requirements for cancer pain and PO pain.

Pharmacodynamics – Mu opioid receptor

The mu-opioid receptor is encoded by the OPRM1 gene, which is highly polymorphic, and has been extensively studied. An early study involving patients receiving methadone maintenance found A118G (adenine replaced by guanine at codon 118) to be the most common SNP in the OPRM1 gene. The resultant variant receptor had three times the binding affinity for β-endorphin and endogenous opioid. Studies with experimental pain are inconclusive regarding patients who are homozygous for A118G, with findings ranging from increased to decreased pain threshold, to not finding significance.

In the clinical setting, multiple studies demonstrate A118G homozygosity to be associated with increased opioid requirements for both PO and cancer pain. However, many studies have shown decreased PO opioid requirements in patients with A118G homozygosity, or simply failed to show significance of the A118G variant on PO opioid usage.

It is important to note that the available clinical results are often controversial and contradictory, particularly when large populations are examined in association with clinical significance of detected polymorphisms in opioid pathways. Perhaps the most striking study to date is one which evaluated opioid dosage in 2294 patients being treated for cancer pain. In this study, none of the 112 SNPs from 25 candidate genes (including OPRM1, ABCB1, and COMT) showed significant associations with opioid usage.

Conclusion

Pharmacogenomics is a rapidly expanding field, but there is not, as of yet, a sufficient body of evidence to support the use of widespread genetic screening to predict individual responses to pain medications and the risk of adverse side effects (with exception of CYP2D6 genome). Pain perception and response to medications is determined by many common genetic variants, that have yet to be discovered. The future of research will include the continued analysis of these many variants and how they relate to one another for pharmacogenomics to become a part of standard clinical practice. The future success of pharmacogenomic testing will depend upon more extensive sequencing strategies, and the characterization of rare mutations with definite biological impact on treatment response, adverse effects, and pain pathology.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Eichelbaum M, Ingelman-Sundberg M, Evans WE. Pharmacogenomics and individualized drug therapy. Annu Rev Med 2006;57:119-37.
2. Mignat C, Wille U, Ziegler A. Affinity profiles of morphine, codeine, dihydromorphine and their glucuronides at opioid receptor subtypes. Life Sci 1995;56:793-9.
3. Zanger UM, Raimundo S, Eichelbaum M. Cytochrome P450 2D6: Overview and update on pharmacology, genetics, biochemistry. Naunyn Schmiedebergs Arch Pharmacol 2004;369:23-37.
4. Dahl ML, Johansson I, Bertilsson L, Ingelman-Sundberg M, Sjoqvist F. Ultrarapid hydroxylation of debrisoquine in a Swedish population. Analysis of the molecular genetic basis. J Pharmacol Exp Ther 1995;274:516-20.
5. Gasche Y, Daali Y, Fathi M, Chiappe A, Cottini S, Dayer P, et al. Codeine intoxication associated with ultrarapid CYP2D6 metabolism. N Engl J Med 2004;351:2827-31.
6. Voronov P, Przybylo HJ, Jaganathan N. Apnea in a child after oral codeine: a genetic variant-an ultra-rapid metabolizer. Paediatr Anaesth 2007;17:684-7.
7. Ciszkowski C, Madadi P, Phillips MS, Lauwers AE, Koren G. Codeine, ultrarapid-metabolism genotype, and postoperative death. N Engl J Med 2009;361:827-8.
8. Kelly LE, 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:e1343-7.
9. Koren G, Cairns J, Chitayat D, Gaedigk A, Leeder SJ. Pharmacogenetics of codeine poisoning in a breastfed neonate of a codeine-prescribed mother. Lancet (London, England) 2006;368:704.
10. Madadi P, Ross CJ, Hayden MR, Carleton BC, Gaedigk A, Leeder JS, et al. Pharmacogenetics of neonatal opioid toxicity following maternal use of codeine during breastfeeding: A case-control study. Clin Pharmacol Ther 2009;85:31-5.
11. Crews KR, Gaedigk A, Dunnenberger HM, 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;95:376-82.
12. VanderVaart S, Berger H, Sistonen J, Madadi P, Matok I, Gijsen VM, et al. CYP2D6 polymorphisms and codeine analgesia in postpartum pain management: A pilot study. Ther Drug Monit 2011;33:425-32.
13. Enggaard TP, Poulsen L, Arendt-Nielsen L, Brosen K, Ossig J, Sindre SH. The analgesic effect of tramadol after intravenous injection in healthy volunteers in relation to CYP2D6. Anesth Analg 2006;102:146-50.
14. Poulsen L, Arendt-Nielsen L, Brozen K, Sindrup SH. The hypoalgesic effect of tramadol in relation to CYP2D6. Clin Pharmacol Ther 1996;60:636-44.
15. Stamer UM, Musshoff F, Kobilay M, Madea B, Hoef H, Stuber F. Concentrations of tramadol and O-desmethyltramadol enantiomers in different CYP2D6 genotypes. Clin Pharmacol Ther 2007;82:41-7.
16. Stamer UM, Stuber F, Mudas T, Musshoff F. Respiratory depression with tramadol in a patient with renal impairment and CYP2D6 gene duplication. Anesth Analg 2008;107:926-9.
17. Orliaguet G, Hamza J, Couloigner V, Denouyele F, Loriot MA, Broly F, et al. A case of respiratory depression in a child with ultrarapid CYP2D6 metabolism after tramadol. Pediatrics 2015;135:e753-5.
18. Stamer UM, Lehnen K, Hothker F, Bayerer B, Wolf S, Hoef H, et al. Impact of CYP2D6 genotype on postoperative tramadol analgesia. Pain 2003;105:231-8.
19. Slanar O, Dupal P, Matouskova O, Vondrackova H, Pakfo P, Perlik F. Tramadol efficacy in patients with postoperative pain in relation to CYP2D6 and MDR1 polymorphisms. Bratisl Lek Listy 2012;113:152-5.
20. Kharasch ED, Walker A, Isollerranan N, Hoffer C, Sheffells P, Thummel K, et al. Influence of CYP3A5 genotype on the pharmacokinetics and pharmacodynamics of the cytochrome P4503A probes alfentanil and midazolam. Clin Pharmacol Ther 2007;82:410-26.
21. Takashina Y, Naito T, Mino Y, Yagi T, Ohnishi K, Kawakami J. Impact of CYP3A5 and ABCB1 gene polymorphisms on fentanyl pharmacokinetics and clinical responses in cancer patients undergoing conversion to a transdermal system. Drug Metab Pharmacokinet 2012;27:414-21.
22. Dong ZL, Li H, Chen EQ, Hu Y, Wu SJ, Tang YY, et al. Effect of CYP3A4*1G on the fentanyl consumption for intravenous patient-controlled analgesia after total abdominal hysterectomy in Chinese Han population. J Clin Pharm Ther 2012;37:135-42.
23. Madadi P, Hildebrandt D, Gong IY, Schwarz UI, Ciszkowski C, Ross CJ, et al. Fatal hydrocodone overdose in a child: Pharmacogenetics and drug interactions. Pediatrics 2010;126:e986-9.
24. Candioti KA, Yang Z, Rodriguez Y, Crescimone A, Sanchez GC, Takacs P, et al. The impact of CYP2D6 genetic polymorphisms on postoperative morphine consumption. Pain Med 2009;10:799-805.
25. Tzvetkov MV, dos Santos Pereira JN, Meineke I, Saadatmand AR, Stingl JC, Brockmoller J. Morphine is a substrate of the organic cation transporter OCT1 and polymorphisms in OCT1 gene affect morphine pharmacokinetics after codeine administration. Biochem Pharmacol 2013;86:666-78.
26. Tzvetkov MV, Saadatmand AR, Lortsch J, Tegeder I, Stingl JC, Brockmoller J. Genetically polymorphic OCT1: Another piece in the puzzle of the variable pharmacokinetics and pharmacodynamics of the opioidergic drug tramadol. Clin Pharmacol Ther 2011;90:143-50.
27. Fukuda T, Chidambaran V, Mizuno T, Venkatassaubramanian R, Ngamprasertwong P, Olbrecht V, et al. OCT1 genetic variants influence the pharmacokinetics of morphine in children. Pharmacogenomics 2013;14:1141-51.
28. Venkatassaubramanian R, Fukuda T, Niu J, Mizuno T, Chidambaran V, Vinks AA, et al. ABC2C3 and OCT1 genotypes influence pharmacokinetics of morphine in children. Pharmacogenomics 2014;15:1297-309.
29. Kircheiner J, Stormer E, Meisel C, Steinbach N, Roots I, Brockmoller J. Influence of CYP2C9 genetic polymorphisms on pharmacokinetics of celecoxib and its metabolites. Pharmacogenomics 2003;13:473-80.
30. Bae JW, Kim JH, Choi CJ, Kim MJ, Kim HJ, Byun SA, et al. Effect of CYP2C9*3 allele on the pharmacokinetics of naproxen in Korean subjects. Arch Pharm Res 2009;32:269-73.
31. Carbonell N, Verstuyft C, Massard J, Letierce A, Cellier C, Deforges L, et al. CYP2C9*3 Loss-of-Function Allele Is Associated With Acute Upper Gastrointestinal Bleeding Related to the Use of NSAIDs Other Than Aspirin. Clin Pharmacol Ther 2010;87:695-8.
32. Pilotto A, Seripa D, Franceschi M, Scarcelli C, Colaizzo D, Grandone E, et al. Genetic susceptibility to nonsteroidal anti-inflammatory drug-related gastroduodenal bleeding: Role of cytochrome P450 2C9 polymorphisms. Gastroenterology 2007;133:465-71.
33. Ma J, Yang XY, Qiao L, Liang LQ, Chen MH. CYP2C9 polymorphism in non-steroidal anti-inflammatory drugs-induced gastropathy. J Dig Dis 2008;9:79-83.
34. Vonkeman HE, van de Laar MA, van der Palen J, Brouwers JR, Vermes I. Allele variants of the cytochrome P450 2C9 genotype in white subjects from The Netherlands with serious gastroduodenal ulcers attributable to the use of NSAIDs. Clin Ther 2006;28:1670-6.
35. Blanco G, Martinez C, Ladero JM, Garcia-Martin E, Taxonera C, Gamito FG, et al. Interaction of CYP2C8 and CYP2C9 genotypes modifies the risk for nonsteroidal anti-inflammatory drugs-related acute gastrointestinal bleeding. Pharmacogenet Genomics 2008;18:37-43.
36. Zwisler ST, Enggaard TE, Noehr-Jensen L, Mikkelsen S, Verstuyft C, Beccuemeont L, et al. The antinociceptive effect and adverse drug reactions of oxycodone in human experimental pain in relation to genetic variations in the OPRM1 and ABCB1 genes. Fundam Clin Pharmacol 2010;24:517-24.
37. Mamie C, Rebsamen MC, Morris MA, Morabia A. First evidence of a polygenic susceptibility to pain in a pediatric cohort. Anesth Analg 2013;116:170-7.
38. Candioti K, Yang Z, Xue L, Zhang Y, Rodrigue Y, Wang L, et al. Single-nucleotide polymorphism C343ST in the ABCB1 gene is associated with opioid consumption in postoperative pain. Pain Med 2013;14:1977-84.
39. Campa D, Gioia A, Tomei A, Poli R, Barale R. Association of ABCB1/MDR1 and OPRM1 gene polymorphisms with morphine pain relief. Clin Pharmacol Ther 2008;83:559-66.
40. Lortsch J, von Hentig N, Freyhagen R, Griessinger N, Zimmermann M, Doehring A, et al. Cross-sectional analysis of the influence of currently known pharmacogenetic modulators on opioid therapy in outpatient pain centers. Pharmacogenet Genomics 2009;19:429-36.
41. Park HJ, Shin H, Ryu SH, Lee HS, Park CS, Kang HJ. Genetic polymorphisms in the ABCB1 gene and the effects of fentanyl in Koreans. Clin Pharmacol Ther 2007;81:539-46.
42. Biesiada J, Chidambaran V, Wagner M, Zhang X, Martin LJ, Meller J, et al. Genetic risk signatures of opioid-induced respiratory depression following pediatric tonsillectomy. Pharmacogenomics 2014;15:1749-62.
43. Sadhasivam S, Chidambaran V, Zhang X, Meller J, Esslinger H, Zhang K, et al. Opioid-induced respiratory depression: ABCB1 transporter pharmacogenetics. Pharmacogenomics J 2015;15:119-26.
44. Lee MG, Kim HJ, Lee KH, Choi YS. The Influence of Genotype Polymorphism on Morphine Analgesic Effect for Postoperative Pain in Children. Korean J Pain 2016;29:34-9.
45. Zwisler ST, Enggaard TE, Mikkelsen S, Verstuyft C, Beccuemoont L, et al. Lack of association of OPRM1 and ABCB1 single-nucleotide polymorphisms to oxycodone response in postoperative pain. J Clin Pharmacol 2012;52:234-42.
46. Sia AT, Sng BL, Lim EC, Law H, Tan EC. The influence of ATP-binding cassette sub-family B member-1 (ABCB1) genetic polymorphisms on acute and chronic pain after intrathecal morphine for caesarean section: A prospective cohort study. Int J...
Gray, et al.: Pharmacogenomics of analgesics in anesthesia

Obstet Anesth 2010;19:254-60.

47. Berthele A, Platzer S, Jochim B, Boecker H, Buettner A, Conrad B, et al. COMT Val158Met genotype affects the mu-opioid receptor system in the human brain: Evidence from ligand-binding, G-protein activation and preproenkephalin mRNA expression. Neuroimage 2005;28:185-93.

48. Zubieta JK, Heitzeg MM, Smith YR, Bueller JA, Xu K, Xu Y, et al. COMT val158met genotype affects mu-opioid neurotransmitter responses to a pain stressor. Science (New York, NY) 2003;299:1240-3.

49. Rakvag TT, Klepstad P, Baar C, Kvam TM, Dale O, Kaasa S, et al. The Val158Met polymorphism of the human catechol-O-methyltransferase (COMT) gene may influence morphine requirements in cancer pain patients. Pain 2005;116:73-8.

50. De Gregori M, Garbin G, De Gregori S, Minella CE, Bugada D, Lisa A, et al. Genetic variability at COMT but not at OPRM1 and UGT2B7 loci modulates morphine analgesic response in acute postoperative pain. Eur J Clin Pharmacol 2013;69:1651-8.

51. Nackley AG, Shabalina SA, Tchivileva IE, Satterfield K, Korchynskyi O, Makarov SS, et al. Human catechol-O-methyltransferase haplotypes modulate protein expression by altering mRNA secondary structure. Science (New York, NY) 2006;314:1930-3.

52. Diatchenko L, Nackley AG, Slade GD, Bhalang K, Belfer I, Max MB, et al. Catechol-O-methyltransferase gene polymorphisms are associated with multiple pain-evoking stimuli. Pain 2006;125:216-24.

53. Kim H, Mittal DP, Iadarola MJ, Dionne RA. Genetic predictors for acute experimental cold and heat pain sensitivity in humans. J Med Genet 2006;43:e40.

54. Rakvag TT, Ross JR, Sato H, Skorpen F, Kaasa S, Klepstad P. Genetic variation in the catechol-O-methyltransferase (COMT) gene and morphine requirements in cancer patients. Mol Pain 2008;4:64.

55. Ross JR, Riley J, Taegtmeyer AB, Sato H, Grettson S, du Bois RM, et al. Genetic variation and response to morphine in cancer patients: Catechol-O-methyltransferase and multidrug resistance-1 gene polymorphisms are associated with central side effects. Cancer 2008;112:1390-403.

56. Sadhasivam S, Chidambaran V, Olbrecht VA, Eftiterfield K, Korchynskyi O, Makarov SS, et al. Human micro-opioid receptor gene (OPRM1) is associated with pressure pain sensitivity in patients undergoing painful cosmetic surgery. Pain 2009;5:32.

57. Sadhasivam S, Chidambaran V, Olbrecht VA, Eftiterfield K, Korchynskyi O, Makarov SS, et al. Human micro-opioid receptor gene (OPRM1) is associated with pressure pain sensitivity in patients undergoing painful cosmetic surgery. Pain 2009;5:32.

58. Sadhasivam S, Chidambaran V, Olbrecht VA, Eftiterfield K, Korchynskyi O, Makarov SS, et al. Human micro-opioid receptor gene (OPRM1) is associated with pressure pain sensitivity in patients undergoing painful cosmetic surgery. Pain 2009;5:32.

59. Sadhasivam S, Chidambaran V, Olbrecht VA, Eftiterfield K, Korchynskyi O, Makarov SS, et al. Human micro-opioid receptor gene (OPRM1) is associated with pressure pain sensitivity in patients undergoing painful cosmetic surgery. Pain 2009;5:32.

60. Sadhasivam S, Chidambaran V, Olbrecht VA, Eftiterfield K, Korchynskyi O, Makarov SS, et al. Human micro-opioid receptor gene (OPRM1) is associated with pressure pain sensitivity in patients undergoing painful cosmetic surgery. Pain 2009;5:32.

61. Sadhasivam S, Chidambaran V, Olbrecht VA, Eftiterfield K, Korchynskyi O, Makarov SS, et al. Human micro-opioid receptor gene (OPRM1) is associated with pressure pain sensitivity in patients undergoing painful cosmetic surgery. Pain 2009;5:32.