Special Article

Do We Need Perioperative Pharmacogenetic Testing?

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Multiple drugs with various mechanisms of actions are used simultaneously during anesthetic practice. Even if the same dose of drug is administered, diverse individual responses usually occur. These different responses might relate to their pharmacogenetics variation. The pharmacogenetics research network has established a pharmacogenetics knowledge base in order to collect, encode, and disseminate knowledge about the impact of human genetic variations on drug response. For perioperative period, opioids are the common drugs used with various individual responses. This review shows the pharmacogenetic aspects of four common opioids: morphine, fentanyl, codeine and oxycodone, and their future trends for perioperative pharmacogenetic testing.

Keywords: Pharmacogenetics, Anesthesia, Opioid

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There was a report of prolonged apneic episodes after suxamethonium administration in early 1950's; the Lancet suggested a genetic basis which related to this prolonged apneic condition[1]. The pharmacogenetics studies are continued by many researchers after completion of the Human Genome Project in 2003, the pharmacogenetics research network has established a pharmacogenomics knowledge base [PharmGKB][2]. The purposes of PharmGKB, supported by some reports, are to collect, encode, and disseminate knowledge about the impact of human genetic variations on drug response, curate primary genotype and phenotype data, annotate gene variants and gene-drug disease relationships, and summarize important pharmacogenetic genes and drug pathways[2-5].

In 2009, the Clinical Pharmacogenetics Implementation Consortium [CPIC] established a level of evidence framework for clinical implementation of pharmacogenetics[6]. The CPIC rating schemes are defined in Table 1 and 2[5,6]. To date, pharmacogenetic information has been inserted into the drug information leaflet in the United States of America and some European countries[3].

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Opioids in Thailand and Pharmacogenetics

Here are some opioids in Thailand with their pharmacogenetic reports.

Morphine

Patient's experience of pain and analgesia can be modified by intrinsic factors (age, gender, genetics) and extrinsic factors (cultures, beliefs)[7]. Morphine is one favorable choice of treatment to relieve severe acute and chronic pain[8]. Clinically, patient's responses to morphine treatments are unpredictable; genetic variations are known as one of the influent factors[5,8]. The genetic polymorphisms of some genes can affect pharmacokinetics and pharmacodynamics of morphine as the followings:

Gene polymorphisms affecting pharmacokinetics

1) Drug transporters

Morphine is a substrate for P-glycoprotein [P-gp], an efflux transporter, belonging to the ATP-binding cassette [ABC] family, encoded by the ABCB1 gene[7,8]. Previous observational studies in cancer patients demonstrated an association between *ABCB1* polymorphisms and patient's analgesic responses or morphine requirements. Bastami et al showed lower doses of opioid requirements for pain relief in homozygous patients for ABCB1 1236T and 3435T[9]. But a current study revealed no association between ABCB1 polymorphisms and patient's analgesic

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Table 1. Clinical Pharmacogenetics Implementation Consortium [CPIC] three-tier scheme; the quality of evidence linking drug-related phenotypes to specific genetic variations*

Quality of evidence	
1	Includes consistent results from well-designed, well-conducted studies
2	Sufficient to determine the effects, but the number, quality, or consistency of the individual studies limit the strength of the evidence, by the inability to generalise to routine practice, or by the indirect nature of the evidence
3	Insufficient to assess the effects on health outcomes because of the limited number of studies, insufficient power of the studies, important flaws in their design or in the way they were conducted, gaps in the chain of evidence, or lack of information

Adapted from Relling MV, Gardner EE, Sandborn WJ, Schmiegelow K, Pui CH, Yee SW, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for thiopurine methyltransferase genotype and thiopurine dosing. Clin Pharmacol Ther 2011;89:387-91[6]

Table 2. Clinical Pharmacogenetics Implementation Consortium [CPIC] three-tier scheme; strength of recommendations*

Level of evidence	
A	Strong recommendation for the statement
B	Moderate recommendation for the statement
C	Optional recommendation for the statement

Adapted from Relling MV, Gardner EE, Sandborn WJ, Schmiegelow K, Pui CH, Yee SW, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for thiopurine methyltransferase genotype and thiopurine dosing Clin Pharmacol Ther 2011;89:387-91[6]

responses[10].

Another transporter is organic cation transporters 1 [OCT1]. This transporter is involved in absorption, distribution, and excretion of organic cations[11]. This polymorphisms influences morphine disposition and hepatic metabolism. Fukada et al reported lower morphine clearance and higher adverse events in Caucasians than in African-American children. The incidence was related to relatively high allelic frequencies of defective OCT1 variants in Caucasians[12]. Up to now, no strong evidence showed that the OCT1 polymorphisms affected morphine response[8].

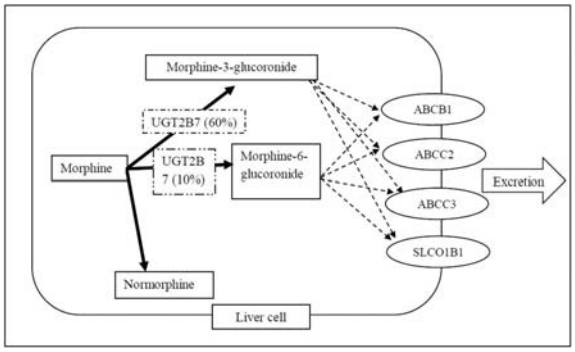
2) Drug metabolism

The UDP-glucuronosyltransferase 2B7 gene encodes for UGT2B7 is the primary enzyme responsible for morphine glucuronidation. Among the UDP-glucuronosyl-transferases [UGTs], the UGT2B7 is the primary enzyme in liver that is responsible for morphine glucuronidation in the morphine metabolism pathway[13]. Approximately 60% of morphine is glucuronidated to morphine-3-glucuronide [M3G] while 5 to 10% is glucuronidated to morphine-6-glucuronide [M6G] as shown in Figure 1[14].

When the UGT2B7 activity increases, the morphine concentrations will decrease and result in inadequate pain control. In contrast, the lower UGT2B7 activity will result in higher blood morphine concentration and some side effects[8]. In 2014, Bastami et al also showed lower doses of opioid requirements for pain relief in homozygous patients for ABCB1 1236T, ABCB1 3435T and UGT2B7 802C[9]. The current evidence of UGT2B7 activity and morphine function is still limited, the further exploration is necessary[8].

Gene polymorphisms affecting pharmacodynamics

Polymorphisms of genes coding receptor functions affect drug potency and efficacy by changing drug affinity, sensitivity and specificity. The mu-opioid receptor [OPRM] gene is also subject to this pharmacodynamic variability. One of the most commonly identified single nucleotide polymorphisms [SNPs] is OPRM A118G. The allele frequency of this polymorphisms range from 2 to 40% depending on



UGT = UDP-glucuronosyltransferase; ABC = ATP-binding cassette family; SLOCO = Solute carrier organic anion transporter family.

Figure 1. Morphine metabolism pathway.

ethnic population[15,16]. Previous studies showed higher intravenous morphine consumption during first postoperative day in the OPRM A118G homozygous patients when compared with heterozygous[17,18]. In the non-opioid system, the catechol-O-methyltransferase [COMT] enzyme is not directly involved in morphine metabolism but it can also modify the efficacy of morphine.

Pain is a complex heterogenous phenotype which can be affected by many factors, these limitations prevent researchers from identifying strong association between genotype and pain response. Thus, there is a moderate level of evidence which links gene variation and morphine response[5]. There is no recommendation to apply pharmacogenetic testing before giving morphine to the patients; however genetic testing may be useful in patients who suffer from morphine side effects or do not respond to potent analgesic treatment[19].

Fentanyl

Fentanyl is one of the most popular drugs used for pain treatments. Wide ranges of inter-individual responses that related to non-genetic and genetic factors have been reported[20]. Some of these variations can be explained by the genetic polymorphisms as the following:

Genetic polymorphisms affecting pharmacokinetics

1) Drug transporter

Fentanyl is also a substrate of P-glycoprotein [P-gp]. The ABCB1-type P-glycoprotein regulates fentanyl passage across the blood-brain barrier. The polymorphisms of ABCB1 gene can cause the adverse central side effect of respiratory depression[20].

2) Drug metabolism

Fentanyl is mostly metabolized to norfentanyl by N-dealkylation which is mediated by CYP450 3A4 and CYP3A5 enzymes[20]. Fentanyl is previously thought to be predominantly metabolized by CYP3A4-mediated N-dealkylation; however, Ziesenitz et al showed that the CYP3A4-mediated N-dealkylation step may not be responsible for a significant part of fentanyl metabolism[21]. When a bolus dose of intravenous fentanyl is given, fentanyl is rapidly distributed from plasma into highly vascularized compartments and then redistributed to muscle and fat tissue. The high extraction rate of fentanyl may be explained by hepatic blood flow instead of the CYP3A4-mediated N-dealkylation pathway[20,21]. Previous studies revealed that CYP3A5*3 caused impaired fentanyl metabolism[22,23]. Patients with CYP3A5*3/3 genotypes had more than three-fold higher risk of central adverse events such as drowsiness, delirium, restlessness, sedation and dyspnea[23]. The European Pharmacogenetic Opioid Study [EPOS], a large cross sectional study, found that the CYP3A4*22 and CYP3A5*3 did not affect the plasma level of fentanyl because they accounted for less than 2% of norfentanyl:fentanyl metabolic ratio[24].

Co-administration of a CYP3A inhibitor with fentanyl should be avoided in order to prevent possible severe side effects of fentanyl[23]. The list of CYP3A inhibitors is shown in Table 3.

Genetic polymorphisms affecting pharmacodynamics

The polymorphisms of mu-opioid receptor (OPRM) 1 gene also affects the fentanyl pharmacodynamics variability. The OPRM1 A118G gene is the most important gene reported with homozygous (GG) subjects tending to be less sensitive to fentanyl[20,25].

Based on current evidence, no recommendation exists stating that pharmacogenetics testing should be applied before administrating fentanyl.

Codeine

Physicians usually prescribe codeine because they believe in the safety of codeine as a weak opioid[5]. However, there were some life threatening or lethal reports related to codeine administration in children and adults[26,27]. Based on the codeine metabolism

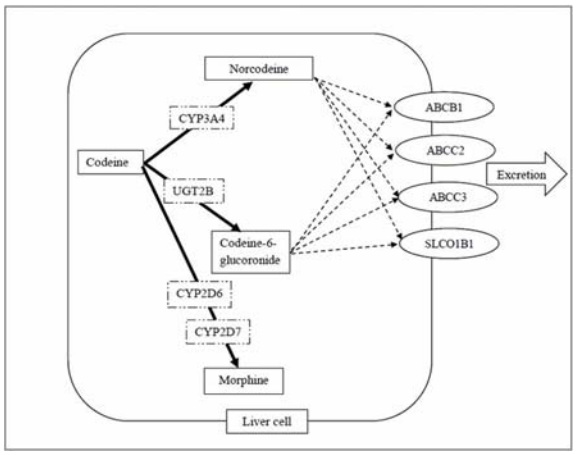
Table 3. Drug interaction table

Inducer/inhibitor	Drugs
CYP 2D6 inhibitors:	bupropion, fluoxetine, paroxetine, quinidine, duloxetine, terbinafine, amiodarone, cimetidine, sertraline, celecoxib, chlorpheniramine, chlorpromazine, citalopram, clemastine, clomipramine, cocaine, diphenhydramine,doxepin, doxorubicin, escitalopram, halofantrine, histamine H1 receptor antagonists, hydroxyzine, levomepromazine, methadone, metoclopramide, mibefradil, midodrine, moclobemide, perphenazine, ranitidine, red-haloperidol, ritonavir, ticlopidine, tripelennamineparoxetine
CYP 2D6 inducers:	dexamethasone, rifampin
CYP 3A4 inhibitors:	indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, nefazodone, saquinavir, telithromycin, aprepitant, erythromycin, fluconazole, grapefruit juice, verapamil, diltiazem, cimetidine, amiodarone, chloramphenicol, ciprofloxacin, delaviridine, diethyl-dithiocarbamate, fluvoxamine, gestodene, imatinib, mibefradil, mifepristone, norfloxacin, norfluoxetine, star fruit, voriconazole
CYP 3A4 inducers:	efavirenz, nevirapine, barbiturates, carbamazepine, glucocorticoids, modafinil, nevirapine, oxcarbazepine, phonobarbital, phenytoin, pioglitazone, rifabutin, rifampin, St. John's wort, troglitazone

Adapted from Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007). "/clinpharm/ddis/clinical-table/" (accessed 02/05/2018) Note- CYP = Cytochrome P family

pathway in Figure 2, approximately 10% of codeine can be converted into morphine by CYP2D6. Then morphine is further metabolized into morphine-6-glucuronide [M6G] and morphine-3-glucuronide [M3G] which can display opioid activity[7,15]. The genetic polymorphism of the genes encoding for CYP450 liver enzymes leads to the various patient's responses to codeine[5,7]. While the poor metabolizers do not respond to codeine therapy, the ultra-rapid metabolizers tend to experience adverse events[5,7]. Thus, CPIC classified the metabolic phenotypes into four groups; (1) ultra-rapid metabolizers [UMs], (2) extensive metabolizers [EMs], (3) intermediate metabolizers [IMs], (4) poor metabolizers [PMs][28]. Previous studies showed relationship between the CYP450 phenotypes and ethnicities. Approximately 5 to 10% of Caucasians are poor metabolizer due to deletions, frameshift or splice-site mutations of the gene[29]. While nearly 30% of Ethiopians have the CYP2D6 gene duplications which are classified as ultra-rapid metabolizers[30]. The UMs have an approximately 50% higher plasma concentrations of morphine, M3G and M6G when compared with EMs[31].

The manufacturers of codeine products have been required to state in the 'Precautions' section of the codeine label of the known risks of prescribing codeine to breastfeeding mothers since 2007, after a death of a breastfed 13-day-old neonate through morphine overdose because his mother was taking codeine[32,33]. In August 2012, the FDA warned of the risk of lethal apneic episodes from codeine use in some children following surgeries. Detailing postmortem findings of two case reports showed CYP2D6 ultra-rapid metabolizer phenotype, which may be responsible for the lethal side effect[34,35]. There is a strong recommendation for CYP2D6 genetic testing for breastfeeding women and young children who receive codeine for pain treatment. The moderate recommendation is also suggested for patients who do



CYP = Cytochrome P family; UGT = UDP-glucuronosyl-transferase; ABC = ATP-binding cassette family; SLOCO = Solute carrier organic anion transporter family

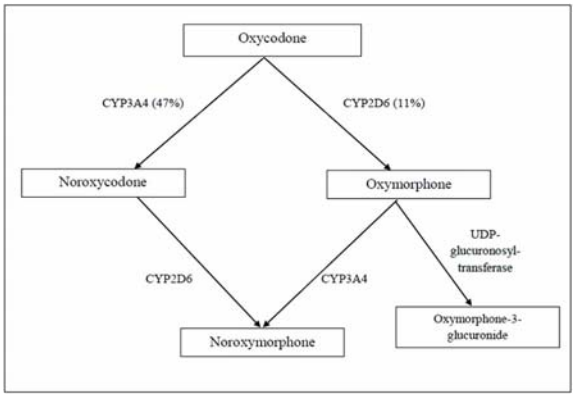
Figure 2. Codeine metabolism pathway.

not respond to high doses of codeine[19]. Recently, the commercial FDA-approved genetic test is available for the CYP2D6 polymorphisms testing in the United States but the genetic testing is not routinely applied[36]. In the United States, prescriptions of codeine for children are avoided. In Thailand, genetic testing is not routinely recommended in clinical use, but the codeine label is also mentioned for prescription with 'Precaution'.

Up to this point, there is strong evidence which links the CYP2D6 gene variation to individual phenotype. However, there has been no randomized clinical trial [RCT] assessing risks and benefits of genetic testing before codeine prescription[5].

Oxycodone

Oxycodone is a semi-synthetic opioid agonist that is approved only for cancer pain treatment in Thailand. Oxycodone undergoes hepatic metabolism through four different pathways. Nearly half of oxycodone is catalyzed by CYP3A4, another 11% is catalyzed by CYP2D6 as shown in Figure 3. While the CYP3A4 pathway shows poor anti-nociceptive effects, polymorphisms of CYP2D6 also impact on various clinical outcomes of oxycodone analgesic effects[37]. More than 70 alleles and 130 genetic variations of CYP2D6 are described along with interethnic variation. Four phenotypic groups are categorized by the number of functional alleles; (1) ultra-rapid metabolizers [UMs], (2) extensive metabolizers [EMs], (3) intermediate metabolizers [IMs], (4) poor metabolizers [PMs][38]. Reduced analgesic effects have been found in the patients who do not have enzyme activity or the PMs. Five to ten percent of the Caucasians are PMs, whereas this phenotype is rarely found in Asians. Highly any variable numbers of PMs are found in the Africans[38]. Sindrup et al and Yang et al mentioned that the defects of the PMs occurred in the final step of endogenous morphine synthesis in the brain[5,39,40]. Another Caucasians 1 to 10% carry on the gene duplications or the ultra-rapid metabolizer [UMs] phenotype[38]. These UMs may have higher analgesic effects but they also have higher risks for mu-opioid-related adverse events. Previous report showed smaller pupil size, more sedative effect in EMs and UMs when compared with PMs[41].



CYP = Cytochrome P family

Figure 3. Oxycodone metabolism pathway.

Although, the level of evidence linking gene variation of CYP2D6 to phenotype of oxycodone response is strong, there is no current RCT on the benefits of genetic testing before oxycodone treatment[5].

Limitation of pharmacogenetic use in Thailand

The pharmacogenetics often refers to the study of each individual genotype and responses to a specific drug. The population specific and inter-population pharmacogenetic studies are needed to investigate the response of Thai or Asian population for opioids. The population-specific studies are the pharmacogenetic studies done in specific ethnic population groups. The inter-population studies are the studies which include subjects of different ethnic backgrounds[42]. For example, high frequency of genetic variants associated with increased CYP2D6 activity was found in Saudi Arabian and Ethiopian but the genetic variants associated with decreased CYP2D6 activity was found in 7 to 10 percent of Caucasians[19].

Other important factors which determine individual drug responses are developmental pharmacokinetics and pharmacodynamics. Human growth is dynamic during the first 2 years of life; there are age-associated changes of body compositions, biotransformation pathways, pharmacological receptors and their functions[43]. For example, the UGT2B7 is present in fetus, and increases at birth. Adult levels of UGT2B7 are reached by age of 2 to 6 months[43]. This is the reason why UGT2B7 developmental pharmacokinetics can play an important role on morphine responses in children. More clinical data of safe perioperative use of opioids are needed for pediatrics[43].

In patients with polypharmacy, the enzyme inducers or enzyme inhibitors play an important role on drug effects. The inhibitors can reduce or inhibit drug effects by competing with other drugs for particular

enzymes; the strong inhibitor can result in more than 80% decrease in drug clearance[44]. Table 3 shows the example of CYP450 drug interaction[44].

There is a recommendation for HLA-B*1502 blood test before prescribe the first carbamazepine prescription in Thailand[45]. In Siriraj Hospital, all patients are screened for HLA-B*1502. This suggestion was based on the higher incidence of Stevens-Johnson syndrome [SJS] and Toxic Epidermal Necrolysis [TEN] of Asian population[46]. Since the perioperative pharmacogenetic testing is a new medical modality in Thailand, more studies are needed for cost-effectiveness guidance of the usage.

Conclusion

To improve peri-operative analgesic outcomes based on patient's pharmacogenetic profile, CYP genotyping before codeine or oxycodone treatment is likely to become strongly recommended. For morphine pharmacogenetics, it is more complicated for pre-operative genetic testing than in codeine and oxycodone group. The large well conducted studies are still needed to identify further useful recommended drug doses and clinical outcomes of drug responses. For further implementation of pharmacogenetic testing, careful consideration is needed. Other considerations include cost, laboratory turn-around time, technicians and clinician availability and the lack of expertise in interpretation among clinicians.

What is already known on this topic?

Implementing genomic medicine can reduce the trial-and-error for each patient.

What this study adds?

This review shows the pharmacogenetic aspects of four common opioids: morphine, fentanyl, codeine and oxycodone, and their future trends for perioperative pharmacogenetic testing.

Potential conflicts of interest

The authors declare no conflict of interest.

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