Pharmacogenomics: New Challenges for Thai Anesthesiologists

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Implementing genomic medicine represents a key method for reducing cost and increasing effectiveness over the traditional trial-and-error treatment through the application of individual genetic analysis to customize health care for each patient. This personalized medicine concept, considering variations of human genome sequence during therapeutic decision making, embodies the essential "P" of the "5Ps" of perioperative medicine and pain management including: 1) personalized, 2) preventive, 3) predictive, 4) participatory and 5) prospective. In the practice of anesthesia, knowing a patient's individual genetic information can help anesthesia providers choose the right medication at the right dose. This individualized prescription practice reduces unnecessary expenses from trial-and-error. However, pharmacogenomic-based medication selection should be considered in only be applied where the evidence and published guidelines support current knowledge.

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The explosion of genetic discoveries since 2003 have introduced all mankind to a new era of personalized genomic medicine. The Human Genome Project has provided an advanced capability for the prediction of both Mendelian and chronic disease susceptibilities, as well as data useful for early individual disease prevention and specific drug treatment. Access to personalized genetic information will enable medical personnel to be aware of a patient's disease-susceptibilities and help them to provide individualized treatments[1]. The international medical community has known that the 'one-size-fits-all' approach is no longer suitable[2].

Medication orders are currently based on patient's demographics information such as weight and age and predicted hepatic and renal clearance. However those factors primarily influence the pharmacokinetics aspect of medication. Two main fields of pharmacology are pharmacokinetics and pharmacodynamics. The former studies what the body does to the drug, and the latter focus on what the drug does to the body. As a result, most of the recommended dose ranges for each medication are usually based on both pharmacokinetic and pharmacodynamics studies. This strategy incorporates most common phenotypes resulting from population studies but overlooks the less common or rare unique variations of human genome. Although most of the variation between individual patients does not have an extensive effect on the majority of medications, some of these genetic differences significantly influence how the patient metabolizes particular drugs. Pharmacogenomics is the study of the role of the genetic influence on drug response. "Pharmaco-genomics or personalized medicine" integrates the use of personal genetic information to select appropriate and optimal therapies based on the context of a patient's genetic analysis. In the future, genomic medicine will play a big role by providing information for doctors to prescribe the right drug, the right dose the first time[2].

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Pharmacogenomics basics

The human genome sequence varies among individuals. Common variations can be separated into five categories as shown in Fig. 1[1].

1) Single nucleotide polymorphisms (SNPs).

2) Microsatellites with varying of dinucleotide repeats.

3) Base insertions.

4) Base deletions.

5) Copy number variation (CNV).

These variations result in alterations of protein functions. As a result, patients' genetic make-up can alter their pharmacokinetics and pharmacodynamics[1]. Pharmacokinetics is divided into 4 components based on 'ADME' scheme; (1) Absorption (2) Distribution (3) Metabolism (4) Excretion as shown in Fig. 2.

The alterations as mentioned above could occur in any steps of individual pharmacokinetic part and lead to significant changes of drug metabolizing enzymes and drug transport molecules. A variant affecting drug transporter proteins could alter drug absorption and distribution rate.

The ABCB1 gene (also known as p-glycoprotein and MDR1) polymorphisms are examples of genetic variants of transporter proteins. This gene is susceptible to single nucleotide polymorphisms. The rs1128503 C>T variant of the ABCB1 gene can affect patients' response to rocuronium by increased duration of action and recovery time[3]. Another example of pharmacokinetic variability is drug metabolizing enzyme variants e.g. cytochrome P450 families. Variants in CYP2C9 have been studied with regard to warfarin dose requirements. Loss of function due to CYP2C9 variants, CYP2C9*2 and CYP2C9*3, is associated with reduced enzyme activity and lower warfarin clearance rates. These variations sometimes lead to undesirable bleeding event from higher serum warfarin concentration despite standard warfarin dosage[4].

In pharmacodynamics the protein function alterations are related with variations of interactions between drug and its target receptors as shown in Fig. 3[1]. The common drug-target interactions are known as coupling, affinity and expression[1]. In general, receptors are the most obvious target of drug responses. Genetic polymorphism of these receptors influences variations of drug-target responses. For example, the polymorphism of angiotensin-I converting enzyme gene results in various responses to ACEI sensitivity[5]. Another classic example of drug-receptor interaction is malignant hyperthermia, a rare life-threatening hypermetabolic syndrome triggered by halogenated inhalation agents and/or succinylcholine[6]. If specific variants in the skeleton muscle RYR1 gene occurs, patients with this mutated gene may produce abnormal uncontrolled release of calcium from skeletal muscle when exposed to inhaled anesthetics and/or succinylcholine.

Cytochrome P-450 genes and enzymes

The names of genes encoding CYP enzymes are the same names as the enzymes themselves. Gene and enzyme nomenclatures are designated with the root symbol CYP for the superfamily, followed by an Arabic number indicating the gene family, a capital letter indicating the subfamily, and another number for the

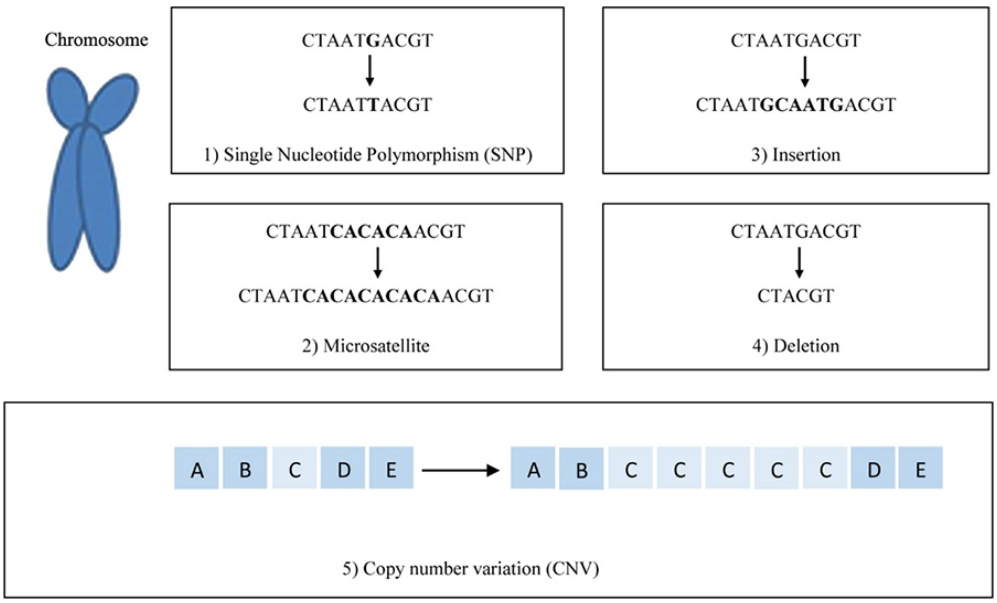

Fig. 1 Categories of common variations of human genetic.

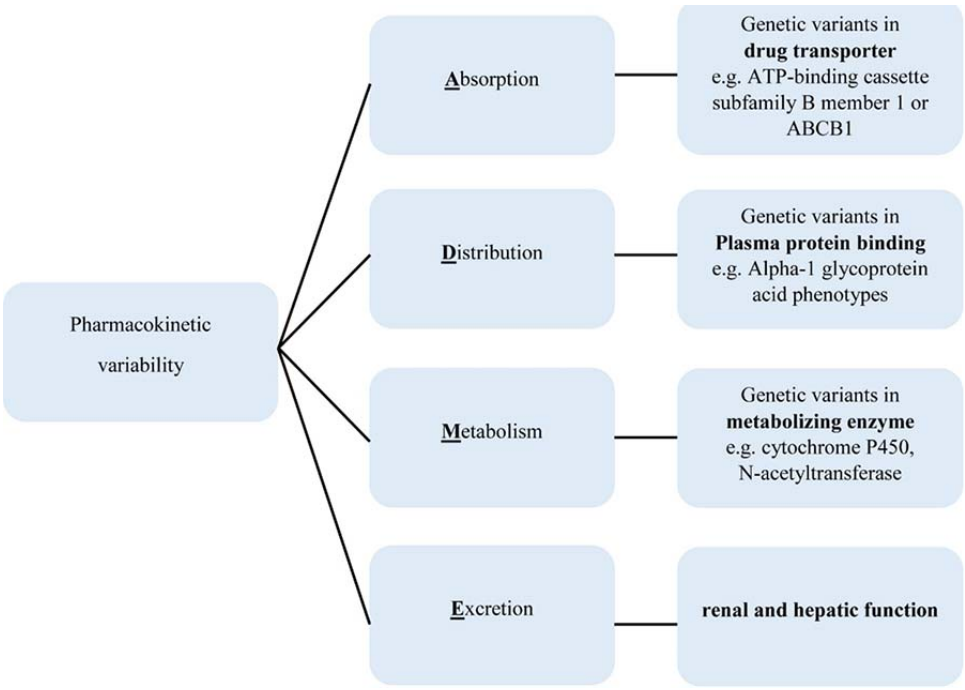

Fig. 2 Four parts of pharmacokinetic variability[1].

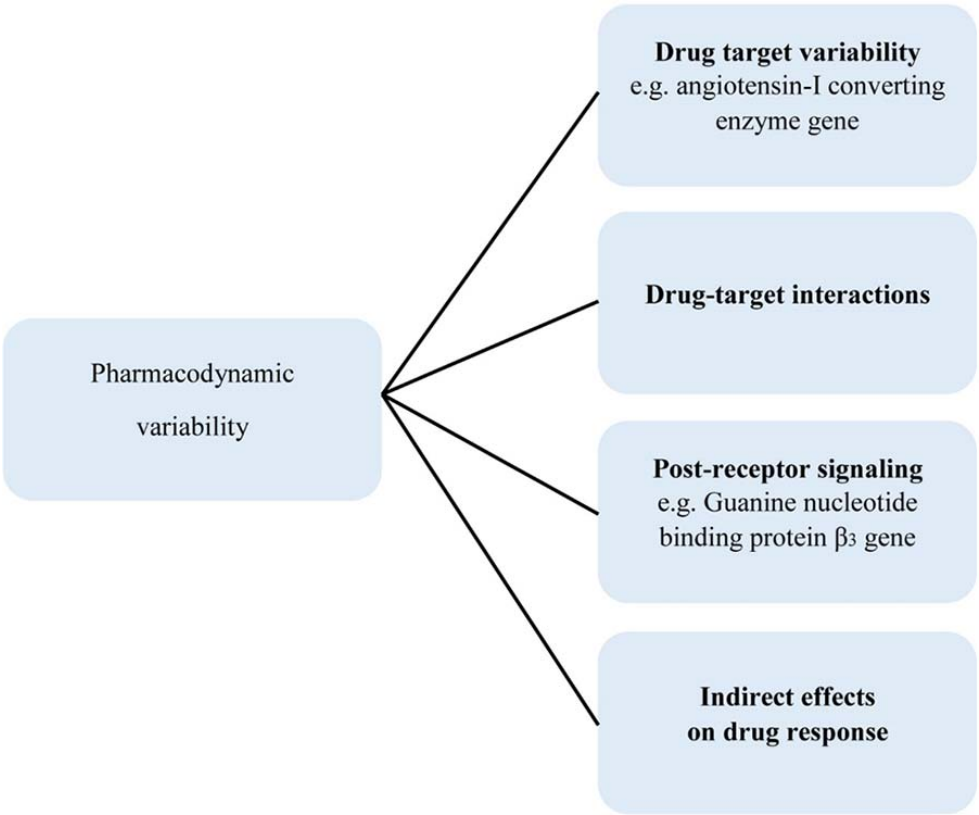

Fig. 3 Four parts of pharmacodynamics variability[1].

individual gene.

The genetic polymorphism of the genes encoding for CYP450 liver enzymes leads to the variations of individual responses to many drugs including anesthetic agents. This CYP450 family of microsomal drug metabolizing enzymes is responsible for phase 1 metabolism (oxidation, reduction, or hydrolysis) of medications. This step converts some parent drugs such as codeine into active metabolites. 5 to 15% of codeine undergo o-demethylation by CYP450 subtype 2D6 (CYP2D6) to morphine (active metabolite) while residual codeine (nearly 80% of an administered dose) is converted to norcodeine and codeine-6-glucoronide as shown in Fig. 4. Certain CYP2D6 genetic polymorphisms may cause various responses to codeine treatment in each patient.

Table 1 demonstrates 4 groups of CYP2D6 phenotypes and genotypes 1) ultra-rapid metabolizers (UMs), the individual having multiple copies of functional allele (5 to 7% of the population), 2) extensive metabolizers (EMs), the individual having at least one functional allele (60%), 3) intermediate metabolizers (IMs), who express at least one reduced functional allele (25%), 4) poor metabolizers (PMs), the individual having two or more nonfunctional alleles (10%)[1,7].

Among the four different phenotypes expressed by CYP2D6 polymorphisms, an ultrarapid metabolizer (who has more active copies of CYP2D6) can convert higher percentage of codeine to morphine (more active metabolite). Therefore even at low dose of codeine, the ultrarapid metabolizer may produce toxic systemic concentrations of morphine. On the other hand, a poor metabolizer (who lacks active copies of CYP2D6) will convert lesser percentage of codeine to morphine. This lower percentage of codeine-to-morphine conversion may result in insufficient pain relief[9].

CYP 2C9 is responsible at least in part for NSAIDs, celecoxib and warfarin metabolism. For this reason, pre-emptive CYP2C9 genotype testing is used for personalized warfarin treatment at some centers in order to reach its therapeutic level as soon as possible and to prevent adverse side effects such as serious bleeding[10]. Another part for intravenous anesthetic agent, in human study show an increased propofol induction requirement in order to make patients who have CYP2C9*2 loss of consciousness[11].

Genetic variability and response to anesthetic agents

Genetic variability and response to inhalation anesthetic agents

The individual differences of minimal alveolar concentration (MAC) of inhaled anesthetic agents are explained by multiple factors such as physiologic factors (age, brain temperature), genetic factors and measurement errors[1]. Ezri et al revealed inter-ethnic sevofurane MAC differences between subjects with red-hair and dark-hair, data showed Jews from the Caucasus Mountain region had the largest MAC. Liem et al found relationship between MC1R gene and

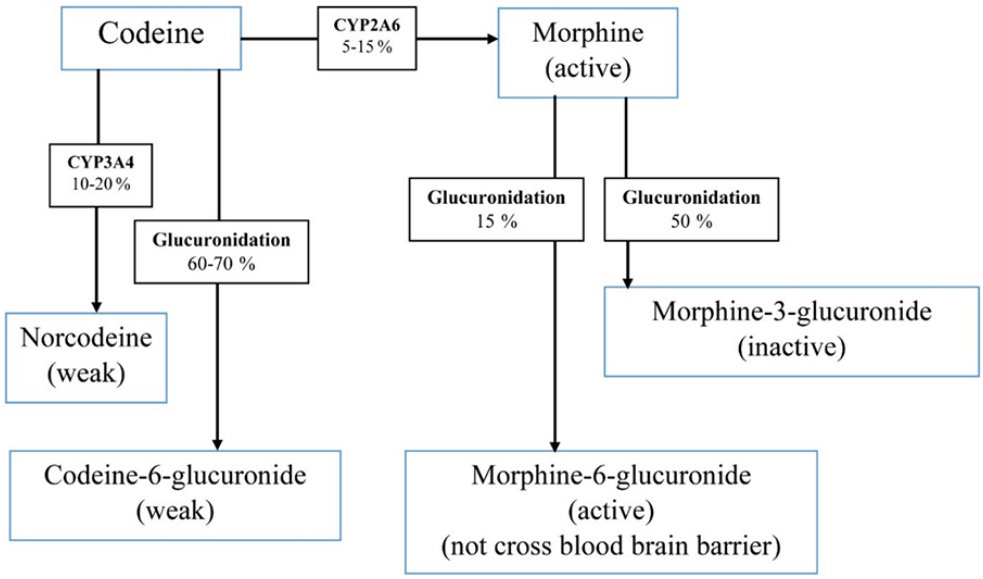

Fig. 4 Codeine metabolism pathway.

Table 1. CYP2D6 phenotype, genotype and recommendation for codeine therapy, adapted from CPIC

Phenotype	Genotype	Phenotype detail	Recommendation for codeine therapy*
Utrarapid metabolizer (UM)	≥3 functional allele	↑ enzyme activity ↑ risk of toxicity	Avoid codeine use due to potential for toxicity
Extensive metabolizer (EM)	at least one functional allele	Normal morphine formation	Use label recommended age- or weight-specific dosing
Intermediate metabolizer (IM)	at least one reduced functional allele	Intermediate enzyme activity, ↑ risk of toxicity morphine formation	Use label-recommended age- or weight-specific dosing If no response, consider alternative analgesics such as morphine or nonopioid.
Poor metabolizer (PM)	two nonfunctional allele	Low or absent enzyme activity, ↓↓↓ morphine formation	Avoid codeine use due to lack of efficacy

* The strength of therapeutic recommendations is "moderate" for intermediate metabolizers, and "strong" for all other metabolizers[8]
Adapted from Crews K.R. et al. Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update Clinical pharmacology and therapeutics. 2014; 95: 376-82[2]

19% difference of desflurane requirement to prevent patients' response to noxious stimuli[12]. However, there are many confounding factors that still unknown such as patients' lifestyles or their environmental factors[13,14]. Data from evolving studies show that this variability appears to also be influenced by individual differences in genes and several receptors. The responsible enzyme for inhalation agent metabolism is CYP2E1[13]. However, current data shows that CYP2E1 variability does not have any clinical impact[10]. NMDA receptors, glycine and sodium channel are candidates to be direct mediators of MAC[1].

Genetic variability and response to opioids

Pain is a complex symptom which is caused by physical and psychological factors. Both intrinsic factors (age, gender, genetics) and extrinsic factors (culture, beliefs) can alter patient's experience of pain and analgesia[15]. To relieve pain, pharmacological management is one favorable choice of treatment.

In current clinical practice, after doctors prescribe standardized pain medication doses, patients demonstrate a wide range of clinical responses varying from no pain relief to complete pain relief to unexpected serious adverse drug events[16]. Possible explanation are the result of genetic polymorphisms; changes to μ-opioid receptor (OPRM) density and function[17]. The OPRM is also subject to pharmacodynamic variability. One of the most commonly identified single nucleotide polymorphisms (SNPs) is ORPM A118G, with an allele frequency of 2 to 40% depending on ethnic population[1,17]. Previous studies claimed that ORPM A118G homozygous patients required more intravenous morphine consumption than heterozygous patients in first postoperative day[18,19]. In an intrathecal opioid trial, ORPM A118G homozygous laboring women were more sensitive to intrathecal fentanyl than heterozygous patients[20].

In opioid distribution and absorption, genetic polymorphism of P-glycoprotein (P-gp) transporter system also have an effect on an individual's opioid pharmacokinetics, including morphine, fentanyl, methadone, and sufentanil[21]. Two SNPs variants, the 2677 and 3435 haplotype in the gene encoding P-gp, have shown associations with opioid side effects[17].

Various results of analgesic treatment, such as codeine, tramadol and dextromethorphan, are predominantly explained by CYP2D6 phase I metabolism, wide range of genetic polymorphism of CYP2D6 results in four categories of clinical phenotypes like previously mentioned in codeine

Table 2. shows some CYP450 enzymes subtypes, CYP2D6, CYP2C9, CYP2C19 and CYP3A4, and common anesthetic drugs interaction

Interaction	CYP2D6	CYP2C9	CYP2C19	CYP3A4
Substrate	Codeine (→ O-desMe)	NSAIDs:	Proton pump	Benzodiazepines:
		Diclofenac	inhibitor:	Diazepam
	Oxycodone	Ibuprofen	Lanzoprazole	Midazolam
	Tramadol	Meloxicam	Omeprazole	
	Ondansetron		Pantoprazole	Calcium channel
	Metoclopramide	S-naproxen		blockers:
		Celecoxib	Propanolol	Amlodipine
	Beta-blocker:	S-warfarin	R-warfarin	Diltiazem
	Propanolol			Nifedipine
	S-Metroprolol	Angiotensin II blocker:		Verapramil
	Timolol	Lorsartan		
				Opioids:
		Sulfonylureas		Alfentanyl
		Glibencamide		Fentnyl
		Glipizide		
				Others:
				Lidocaine
				Ondansetron
				Propanolol

metabolism. In patients receiving codeine, while conventional doses of an active drug cannot treat pain in most polymorphically expressed enzyme poor metabolizers group, the ultra-rapid metabolizers are at risk for severe or fatal adverse drug events[15].

Pseudocholinesterase deficiency

Pseudocholinesterase deficiency is defined as an uncommon disorder of plasma cholinesterase, atypical pseudocholinesterase, butyrylcholinesterase (BCHE), acylcholine acylhydrolase and cholinesterase II deficiency. This condition can be inherited, acquired, or iatrogenic[9]. In 1956, the prolonged duration of action following a dose of intravenous succinylcholine was noted in patients with an inherited deficiency cholinesterase enzyme[21]. Incidence of pseudocholinesterase deficiency ranges from 1: 3,200 to 1: 5,000 individuals. It is more common in the Alaska Natives and Persian Jewish community.

To date, there are more than 20 different mutations in the BCHE gene that have been identified. The A (209A >G) variant or dibucaine resistant and the K variant (1615G >A) are the two most common types[1]. The homozygous A variant are at risk of prolonged apnea following succinylcholine administration. The heterozygous variant for the K and A may experience prolonged muscle relaxation following succinylcholine administration, ranged from 5 minutes to 1 hour[10]. However, pharmacogenomic testing of pseudocholineesterase deficiency is not recommended as routine preoperative testing, rather it is currently used to explain causes of prolonged relaxation[1]. In Siriraj Hospital, the BCHE gene is still cannot be tested.

Malignant hyperthermia

Malignant hyperthermia (MH) is a rare life-threatening hypermetabolic syndrome triggered by halogenated inhalation agents and/or succinylcholine[6]. When MH susceptible patients expose to MH triggering agents, halogenated inhalation agents and/or succinylcholine, uncontrolled calcium releases may lead to hypermetabolic states. The earliest signs that can be detected are tachycardia, increased end-expired carbon dioxide concentration despite increased minute ventilation, followed by muscle rigidity. If untreated, MH can result in death or multi-organ failure such as compartment syndrome of limbs, acute renal failure, congestive heart failure, bowel ischemia[6].

Even though more than 23 mutations that have been found to be associated with MH, the mutation of the RYR1 gene, on chromosome 19, is the most predominant susceptibility[13]. In spite of the knowledge of these genetic links to MH, anesthesiologists currently identify MH susceptible patients by obtaining

a personal history of previous anesthesia experience and a family history of adverse reactions to anesthesia. It is important to obtain this information prior to providing anesthesia to every patient. If there is a suspicion of MH by history, halogenated inhalation agents and/or succinylcholine should be avoided[10].

Incidence of malignant hyperthermia (MH) ranges from 1:10,000 to 1: 250,000 anesthetics[22]. From Thai Anesthesia Incidents Study (THAI Study) in 2005 demonstrated an incidence of of approximated 1: 150,000 individuals[23]. However, estimated the prevalence of the genetic abnormalities for MH susceptibility ranges from 1: 3,000 to 1: 8,500 individuals[22]. To date, exome sequencing data reveals MH genetic susceptibility incidence in 1: 419 individuals[24]. More than 23 mutations that have been found to be associated with MH, the mutation of the RYR1 gene, on chromosome 19q13.1, is the most predominant susceptibility[13]. MH susceptible patients may develop MH crisis at first MH triggering agent exposure. But current data show that patients require three anesthetics before triggering on average[23]. The history of MH crisis free anesthesia events are not guarantee of non-MH susceptibility. However, it is still very important for anesthesia providers to obtain previous anesthetic history and family history of patients before providing anesthesia. No recommendation for DNA testing in general population because of the polygenic determinism and variable penetrance. If there is a suspicion of MH, halogenated inhalation agents and/or succinylcholine should be avoided[10]. In Thailand, intra-operative MH crisis is currently based on clinical diagnosis. Prompt treatments are initiated without any laboratory or genetic testing confirmation.

RYR1 is a challenging gene for genetic screening because it is a large gene with 106 exons[23]. In Siriraj hospital, only 6 selected RYR1 exons are screened. The clinicians have to wait for 1 month to obtain official exon sequencing test results.

Future directions of perioperative pharmacogenomics in Thailand

Routine pre-emptive pharmacogenomics screening of patients would have significant cost implications. Despite decreasing costs to perform testing, the number needed to screen to find a patient that would require intervention is still too large to produce a cost-effective intervention. Thus, pharmacogenomics testing in the general population is not currently recommended in developing country like Thailand due to health care economics concerns. For some high-risk drugs, such as warfarin, the implementation of these projects may improve therapeutic outcomes and individualize drug therapy while at the same time decreasing costs associated with severe adverse drug events. In current Thai anesthesia practice, there is a lot of work to be done in order to incorporate perioperative pharmacogenomics. To promote value-based health care and reduce unnecessary expenses, the pharmacogenomics implementation should be considered in select patients, such as those patients who have previously demonstrated unexpected responses to therapy.

In general population, the implementation of pharmacogenomics should be in conjunction with traditional anesthesia considerations[10].

What is already known on this topic?

Genetic medicine concept helps medical personnel to select proper drug treatment for each patient.

What this study adds?

In the upcoming practice of anesthesia in Thailand, knowing a patient's individual genetic information can help anesthesia providers choose the right medication at the right dose.

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Potential conflicts of interest

None.

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เวชพันธุศาสตร์: ความท้าทายใหม่ของวิสัญญีแพทย์ไทย

ศิริรัตน์ รัตนอาภา, พัชรี ศรีสวัสดิ์

Genomic medicine เป็นแนวคิดสำคัญที่ใช้ในการลดค่าการรักษาพยาบาลและเพิ่มประสิทธิภาพการรักษา โดยการใช้ข้อมูลทางพันธุกรรมของมนุษย์มาช่วย ในพิจารณาเลือกวิธีการรักษาที่เหมาะสมกับผู้ป่วยแต่ละรายแทน การใช้การรักษาแบบลองผิดลองถูกที่ถูกใช้อยู่เดิมในเวชปฏิบัติ การให้การรักษาแบบเฉพาะบุคคลโดยการพิจารณาจากลำดับคู่เบสในสาย DNA (genome sequence) นั้นอาศัยหลัก "5Ps" ในการดูแลผู้ป่วยระหว่างผ่าตัด และการระงับปวด ได้แก่ 1) Personalized (เฉพาะบุคคล) 2) Preventive (ป้องกัน) 3) Predictive (ทำนาย) 4) Participatory (มีส่วนร่วม) 5) Prospective (คาดการณ์) สำหรับเวชปฏิบัติทางวิสัญญี ความรู้เกี่ยวกับข้อมูลทางพันธุกรรมเฉพาะบุคคลนั้นช่วยให้บุคคลากรทางวิสัญญีสามารถเลือกยา และขนาดของยาระงับความรู้สึกได้เหมาะสมกับผู้ป่วยแต่ละราย และช่วยลดค่าใช้จ่ายที่ไม่จำเป็นที่เกิดจากการลองผิดลองถูกในการใช้ยาเพื่อรักษา อย่างไรก็ตามการนำข้อมูลทางเวชพันธุศาสตร์มาประยุกต์ใช้ในประเทศไทย ในปัจจุบันนั้นควรพิจารณาทำในผู้ป่วยที่มีข้อบ่งชี้เฉพาะบางอย่างที่มีข้อมูลความรู้ในปัจจุบันสนับสนุนเท่านั้น