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Pharmacogenetics Variations in Anesthesia

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Abstract

Pharmacogenetics is an emerging discipline that attempted to understand the hereditary basis for differences in responsiveness or inter-individual variation to therapeutic agents. It is the study of variability in drug response as a result of heredity factors. The importance for pharmacogenetics for the clinician is to enable optimum therapeutic efficacy, to avoid toxicity of those drugs whose metabolism is catalyzed by polymorphic isoenzymes, and to contribute to the rational design of new drugs.

The experience of anesthetists suggests that there is great heterogeneity in anaesthetic requirements in the way patients recover from uncomplicated anaesthesia, as well as their requirements for postoperative analgesia. Some of these differences can be explained by genetically determined differences in transport proteins, in drug targets and in enzyme functions. Some environmental factors such as smoking, diet, and other drugs play very important role to interact with genetic factors to modulate drug effects.

Recovery from general anaesthesia is dependent on factors governing drug sensitivity and drug disposition and recovery from a single dose of i.v. anaesthetic agent is dependent on redistribution, whereas recovery after a prolonged infusion is more dependent on metabolism and elimination of the drugs.

Keywords: Pharmacogenetics; Polymorphism; Pharmacokinetics; Receptors; Pharmacodynamics

Introduction

A drug may work well in one person, but poorly or not at all in another. One person may tolerate a drug well, whereas another develops side effects. This fact is as well known as it is unfortunate. These individual differences are largely due to our genome, the genetic blueprint that makes each of us unique. Thanks to new knowledge and techniques, medicine is now able to take greater account of these differences – thus leading to the development of more effective, safer and better tolerated drugs.

Environmental factors, chance and above all the small differences in our genomes make each of us unique. In fact, it has been known for some time that the efficacy and tolerability of drugs vary from one person to the next. Thus, some patients need a lot more or a lot less of a given drug than most people; side effects keep occurring unexpectedly; and sometimes a drug that is usually highly effective does not work at all. Our uniqueness is reflected in our body's response to drugs. Future drugs, it is hoped, will be better adapted to our genetic diversity and dissimilar life circumstances and will be more efficient, more specific and safer. And they will be supported by a battery of fast, simple genetic tests that will enable doctors to select the right drug for their patients' specific needs.

Anesthetists and other clinicians have concentrated on genetic variability that alters drug metabolizing enzymes to explain variation in pharmacokinetic responses to drug therapy. However, it is now apparent that genetic variability can affect many other important proteins such as transporter proteins and receptors. Thus pharmacogenetics plays an important role in genetic variations which is responsible to cause a variable drug response and includes the genetic polymorphism of drug transporters, drug metabolizing enzymes, and drug receptors.

Drug metabolism

Drug metabolism is divided into phase I and phase II reactions [1]. Phase I reactions, including oxidation, reduction, and hydrolysis, introduce a polar group into the molecule, whereas phase II reactions conjugate an endogenous hydrophilic substance with the drug, resulting in more water-soluble compounds. Oxidation plays very important role in metabolism for many drugs which is catalysed by the oxidase system and it comprises of cytochrome P450 (CYP) enzymes [2,3].

It is found in all tissues with the highest concentration in the endoplasmic reticulum of the liver [4]. cytochrome P450 isoenzymes is based upon grouping enzymes and genes into families and subfamilies with the prefix CYP denoting cytochrome P450. It is characterized into CYP2 and CYP2D. Members of the same enzyme/gene family may exhibit more than 40% identity in amino acid sequences, while a subfamily consists of greater than 55% sequence identity. P450 isoenzymes played important role in human hepatic drug metabolism. Their activity is also determined genetically as a consequence of common polymorphisms and it may be inhibited or induced by drugs. The cytochrome P450 enzymes activity can be measured by administration of a probe drug, and it is metabolized by the CYP enzyme under study, followed by measurement of the metabolic ratio. Such phenotyping influencing the activity of the enzyme, such as the presence of a competing substrate, and is sensitive to the overall process of drug metabolism.

In case of genotyping identification of defined genetic mutations on the *CYP* genes that give rise to the specific drug metabolism phenotype. These mutations include genetic alterations that lead to gene duplication, absence of an active protein product, or production of a mutant protein with diminished catalytic capacity.

Genotyping methods require small amounts of blood or tissue,

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and it is not affected by underlying disease or by drugs taken by the patient, and need to be done only once in a lifetime. By screening for genetic variants, an individual's drug metabolism phenotype can be characterized [5]. Other than the P450 genes, some enzymes are also polymorphic, such as alcohol dehydrogenases and acetaldehyde dehydrogenase, as well as dihydropyrimidine dehydrogenase. With respect to the first two enzymes, the clearance of ethanol is significantly affected, ADHB2 giving a higher rate of ethanol metabolism and ALDH2 polymorphism influencing acetaldehyde metabolism. Poor metabolizers for ALDH2 develop flush reactions and anti-abuse like side-effects when drinking ethanol and the number of alcoholics with this genotype is lower.

5-Fluorouracil is metabolized by DPD enzyme, which is relevant to treatment with anticancer drugs. Subjects with impaired enzyme activity caused by inactivating gene mutations suffer from a severely increased risk of adverse reactions, including myelotoxicity and neurotoxicity following 5-fluorouracil administration [6].

Phase II enzymes

Many enzyme families directly conjugate drugs or their oxidative metabolites. There are 15 human uridine diphosphate glucuronosyltransferases (UGTs), broadly classified into the UGT1 (phenol/bilirubin) and UGT2 (steroid/bile) families [7]. Considerable polymorphism in glutathione S-transferase expression has been described and associated with susceptibility to disease, such as cancer and asthma which is disease-causing and disease-modifying factors [8]. Slow acetylators show a greater therapeutic response than fast acetylators to several drugs (i.e. isoniazid, hydralazine) but may be more susceptible to side-effects. Sulfotransferases (STs) catalyse the elimination of acetaminophen and morphine in neonates [9].

The clinical implications of polymorphism of drug metabolizing enzymes are drug toxicity and therapeutic failure. The clinical relevance, however, depends on the therapeutic ratio of the drug [10].

Transporter proteins

Genetic variability influences drug absorption and it forms the basis for slow and rapid drug absorption and the influence of the genetic make-up of an individual is not limited to drug metabolism. Some drugs are actively transported by transporter proteins, of which membrane transporters may play a key role but most drugs or drug metabolites enter the cells by passive diffusion. These transmembrane transporters are members of the large protein family known as ABC (adenosine triphosphate binding cassette) proteins [11] they do not catalyse biotransformation but affect drug bioavailability and can act in conjunction with intracellular drug metabolizing enzymes. P-Glycoprotein is the first cloned and best-characterized ABC protein [12]. At the blood–brain barrier, it may influence the uptake of substrates into the brain: high P-glycoprotein levels may limit the uptake of sufficient amounts of the desired drug into the brain, and reduced P-glycoprotein activity could lead to abnormally increased accumulation in the brain and undesired side-effects of a drug [13].

A second subfamily of ABC proteins is the multi-drug resistance-associated proteins, also known as the multi-specific organic anion transporter [14]. The first protein to be discovered in this category was MRP1, whose over-expression is responsible for the majority of non-P-glycoprotein-mediated multi-drug resistance. There are seven currently known MRPs with uncertain clinical significance. Rifampicin is known to induce human MRP2 [15].

Receptors

Receptor is the most important target for genetic studies when examining the drug response, Genetic variability influences interactions with receptors and this forms the basis for poor or efficient receptor interactions. The polymorphisms in genes encoding receptors relevant to drug treatment of different diseases cause widespread variation in sensitivity to many drugs. For example, individuals with a mutation in the gene encoding prothrombin may have increased risk of cerebral vein thrombosis when using oral contraceptives. Mutations in cardiac potassium channel genes such as HERG (human ether-a-go-go-related gene) and KvLQT1 (chromosome 11 linked LQT gene) may both give susceptibility to drug-induced long QT syndrome, or KCNE2 (a potassium gene encoding MinK-related peptide-1, MiRP1) may give susceptibility to drug-induced arrhythmias. All are of clinical relevance to an anaesthetist [16].

At the genome level, pharmacogenomics aims to identify disease genes and new drug response markers [17]. The role of pharmacogenetics is increasingly recognized by the pharmaceutical industry with research programmes directed at drug discovery and development [18]. Pharmacogenetic data may be used either to design better compounds or to help plan clinical studies. Screening volunteers and patients included in clinical trials may become necessary to minimize adverse events and optimize efficacy. Clinical investigations in various populations will help clarify inter-ethnic differences in drug disposition and response to a given drug. Knowledge of pharmacogenetics should help reduce the time and cost associated with new drug development.

Plasma cholinesterase

The first documented example of inherited variations in anaesthetic drug effects was plasma cholinesterase which will result in prolonged muscle relaxation after succinylcholine [19]. The level and quality of plasma cholinesterase activity (acylcholine-acylhydrolase E.C.1.1.8, butyrylcholinesterase (BChE)) in a patient determines the duration of action of succinylcholine and mivacurium.

Genetic variation is one of several factors determining the activity of cholinesterase in plasma. It is important to be able to diagnose not only the well-known atypical variant but also the low-activity variants such as the H, J, K, and S variants. Using standard enzymatic and inhibition analysis, it is not possible to distinguish between the usual genotype (UU) and genotypes in which one of the quantitative variants, H, J, K, or S, is present in heterozygous combination with the usual gene (UH, UJ, UK, or US) [20]. Molecular biology techniques allowed analysis of the detailed structure of the human BCHE gene. For qualitative variants, a portion of the structural gene responsible for the amino acid sequence of the protein (BChE) is altered. Variants in which there is a marked quantitative reduction in the level of enzymatic activity could result from a structural modification that causes little or no active enzyme being preserved and regulatory defect affecting primarily the rate of enzyme synthesis.

In addition, plasma cholinesterase availability could be decreased, and thus neuromuscular block after succinylcholine lengthened, by competitive interaction with (i) anticholinesterases, including neostigmine, edrophonium, and (ii) other drugs metabolized by plasma cholinesterase, such as etomidate, propanidid, ester local anaesthetics, methotrexate, monoamine oxidase inhibitors, and esmolol [19].

CYP enzymes

CYP families are responsible for phase I metabolism of most drugs.

Enzymes in the CYP2C, CYP2D, and CYP3A subfamilies are most active in metabolizing clinically used drugs [21]. *CYP2C* enzymes eliminate oral hypoglycaemics, warfarin, some antiepileptics, non-steroidal anti-inflammatory drugs, amitriptyline, barbiturates, diazepam, and omeprazole. The most important substrates for CYP2D6 are a number of psychoactive drugs such as antidepressants and neuroleptics, and cardiovascular drugs such as beta-blockers and antiarrhythmics.

Drugs in this class relating to anaesthetic practice include codeine, tramadol, ondansetron, granisteron, and metaraminol [22]. It has been postulated that CYP2D6 poor metabolizers are more susceptible to pain than extensive metabolizers because of a defect in synthesizing endogenous opioids [23]. Postoperative pain treatment with codeine-containing drugs will therefore have limited effect in patients with this trait, whose request for larger doses of codeine could easily be misinterpreted as drug addiction. This genetic variation makes it not surprising that a standardized prescription of codeine for pain relief will result in remarkable variation in the adequacy of pain relief. *CYP2E1* is more of toxicological interest as it has been reported to have a unique capacity to activate many xenobiotics to hepatotoxic (among them acetaminophen) or carcinogenic products [24]. *CYP2E1* is the principal, if not sole human liver microsomal enzyme catalysing defluorination of sevoflurane. It is also the principal, but not exclusive enzyme responsible for the metabolism of methoxyflurane, and is responsible for a significant fraction of isoflurane and enflurane metabolism.

Identification of *CYP2E1* as the major anaesthetic metabolizing enzyme in humans provides a mechanistic understanding of fluorinated ether anaesthetic metabolism and toxicity [25].

CYP3A4 handles drugs such as local anaesthetics, a number of antiepileptics, steroid hormones, systemic antifungals, midazolam, erythromycin, alfentanil, and possibly also fentanyl and sufentanil [26]. As human alfentanil metabolism is catalysed predominantly, if not exclusively by CYP3A3/4 (electrophoretically inseparable and immunochemically indistinguishable), inter-individual variability in human alfentanil disposition and alfentanil drug interactions may be attributable to individual differences in CYP3A3/4 activity. Variability in CYP3A3/4 expression may have genetic and environmental (age, sex, disease state, concomitant drug administration) components, and the degree of variability is sufficient to explain the 10-fold range in alfentanil clearance observed clinically [27].

P-Glycoprotein, a member of the adenosine triphosphate is expressed in the capillary endothelium of the blood–brain barrier and in many other cell membranes such as intestinal enterocytes and biliary and renal epithelial cells [28]. Block of P-glycoprotein allows enhanced central nervous system (CNS) entry of some drugs, offering new possibilities to explain CNS-related adverse effects during the administration of drugs that are substrates of P-glycoprotein and, furthermore, to manipulate the CNS entry of drugs whose target is located in the brain [29]. As new drugs are introduced into clinical practice, it will be important to assess whether they are P-glycoprotein substrates or inhibitors to assess their potential for drug interaction. Inter-individual variability in P-glycoprotein activity is now recognized, which may at least partially depend on genetic polymorphism. Homozygosity for an allele associated with deficient P-glycoprotein activity occurs in 24% of white people [30].

GABAA receptor

A new class of human GABAA receptor subunit that confers insensitivity to the potentiating effects of i.v. anaesthetic agents on gabaminergic transmission has been identified. Wilke and colleagues identified the gene, symbolized GABRE, coding for class epsilon of the GABAA receptor (gene map locus Xq28) [31].

Genetic variation in the gene encoding for this subunit of a GABA-receptor may be of importance for the sensitivity to diazepam, barbiturates and propofol, or susceptibility to alcohol addiction [32]. Volatile anaesthetics act through a different site on the GABAA receptor molecule from the i.v. anaesthetics, although the nature and location of that site remains unclear. Volatile anaesthetics and propofol show no significant selectivity between any receptor subtype. The effects and side-effects of any drug will significantly depend on the genetic impact on its pharmacokinetics and pharmacodynamics. An active drug which is metabolized slowly by a person with increased receptor sensitivity may cause toxic effects, while an active drug which is metabolized extensively by a person with reduced receptor sensitivity, may have a reduced effect [33].

An understanding of the CYP system and its substrates is also a key factor in the prevention of important drug–drug interactions, either as a result of enzyme induction or inhibition. The former may take some time to develop and usually reduces the effect of the drug involved, while the latter takes place instantly with side-effects as a common result [34].

Future Prospects

Routine screening of patients before starting pharmacotherapy would have significant cost implications. Cost savings associated with toxic episodes or therapeutic failure and subsequent intervention could be expected in most specialties. But in anaesthesia, we administer drugs to a large number of patients, often once only, and frequently only briefly after the patient has presented for treatment. In this setting, a genetic screening programme is unlikely to represent a cost-effective method for reducing morbidity. Pharmacogenetics will have its application in clinical research [35]. When designing clinical trials, genotype can be used a priori, as an exclusion criterion. With this methodology, the study group can be smaller and more homogeneous, though less representative. Phase I trials can thus be designed for representative populations of the principal metabolic patterns.

Conclusions

Pharmacogenetics is in initial stage of clinical practices. It is very likely that its contribution to new drug development will become reality. Common polymorphisms in drug targets dictate that DNA sequence variations will be taken into account in the genomic screening processes aimed at new drug development. This will provide new insights for the development of medications that target critical pathways in disease pathogenesis, and medications that can be used to prevent diseases in individuals who are genetically predisposed to them. This represents a migration from the traditional strategy of trying to develop medications that are safe and effective for every member of the population, but one that is a pharmacological long shot because of highly potent medications, genetically diverse patients, and diseases that have heterogeneous subtypes. It is anticipated that, over the next decade, the Human Genome Project, coupled with DNA array technology, high-throughput screening systems and advanced bioinformatics, will permit rapid elucidation of complex genetic components of human health and disease. Despite its promise, genomics has yet to make a major impact on drug development processes.

Although pharmacogenetics is unlikely to change the way anaesthesia is practised today it may help to elucidate inter-patient

variability in drug response. We will, undoubtedly, see its impact on other specialties on new drug development, and in drug delivery systems.

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