

Single Nucleotide Polymorphisms, Drug Metabolism and Untoward Health Effects

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Abstract

Adverse drug reactions and therapeutic treatment failures are major problems. These untoward health effects often occur because single nucleotide polymorphisms (SNPs) affect the absorption and metabolism of drugs. Although there has been significant progress in defining the effect of SNPs on drug metabolism and treatment failures, there is less information on SNPs and adverse drug reactions. To fully understand the relationship between SNPs and untoward health effects there is a need for more detailed information on overlapping and redundant enzyme substrates, and polymorphisms in drug transporters or Phase I and II metabolic enzymes.

Introduction

Untoward health effects caused by the administration of pharmaceuticals can be divided into adverse drug reactions (ADRs) and treatment failures (TFs). Adverse drug reactions (ADRs) include a wide variety of toxic drug reactions that occur during treatment and excludes non-therapeutic over dosage and treatment failures or loss of efficacy (Anonymous "Drug Toxicity"). ADRs cause more than 2 million hospitalizations and 100,000 deaths each year in the United States (Shastry) making adverse drug reactions between the 4th and 6th leading cause of death (Ingelman-Sundberg). In 2000, overall costs for drug related morbidity and mortality exceeded 177 billion dollars and represented 10% of the total health care costs (Ernst and Grizzle). Loss of efficacy that results in therapeutic failures (TFs) is a persistent problem. Often physicians must utilize another drug or modify dosage to increase efficacy. This may result in significant delays in achieving successful treatment. At the present time, the frequency of treatment failures is unknown.

It is now possible to explore the role of genetic factors in drug metabolism. Data from the Human Genome Project identified single nucleotide polymorphisms (SNPs) in drug metabolism genes. Polymorphisms occur when a single nucleotide is replaced in a DNA segment. For example, the nucleotide cytosine may be replaced with a thymine. If SNPs reside in a coding region, there is an alteration in the amino acid sequence of an enzyme that directly or indirectly influences function (Anonymous "Snps: Variation on a Theme"). When the polymorphism occurs in the promoter site, transcription and translation may be accelerated, reduced or lost (Anonymous "Snps: Variation on a Theme"). It follows that individuals within a population may have different abilities to transport drugs across membranes, and metabolize or excrete drugs in a water soluble form. Using SNP haplotypes or genotypes, it may be possible to classify patients into groups of poor metabolizers with an ADR risk or patients with altered drug metabolism affecting efficacy. Since genotyping would allow the physician to choose a drug regimen with the lowest risk for ADRs and the proper dose needed for efficacy, it may herald the advent of individualized pharmaceutical medicine and therapeutics. This concept has already impacted Food and Drug administration (FDA) and biotechnology firms. In 2003, the FDA issued "Draft guidance for Industry Pharmacogenomic Data Submission" and package inserts in select pharmaceuticals (e.g. irinotecan) contain pharmacogenomic information (Giacomini et al.).

The absorption, distribution, metabolism and excretion of xenobiotics are complex processes. Absorption and distribution is predicated on the ability to cross lipid membranes. In most cases, transporter proteins move hydrophobic compounds across the membrane into the cell. To

maintain cellular homeostasis, efflux pumps are used to remove excess drugs or toxic materials. Drug metabolism is dependent on Phase I and Phase II chemical reactions mediated by cytochrome p450 (CYP450) isoenzymes in the liver. The Phase I isoenzymes introduce or expose functional groups in the drug as a consequence of oxidation, reduction or hydrolysis reactions (Klassen). During Phase II reactions catalytic enzymes such as glutathione S-transferase (GST), UDP glucuronosyltransferase (UGT) and thiopurine S-methyltransferase (TPMT) link the modified metabolites to glucuronide, glutathione, and sulfate or select amino acids. The goal of the Phase II reactions is to create water soluble conjugates that can be eliminated from the body in bile and urine.

Drug absorption and transporters

Absorption, distribution and drug toxicity are controlled by two transporter protein super families. One family of solute carrier proteins transports molecules into the cell. Conversely, the ATP binding cassette (ABC) transporter protein family (Leslie, Deeley and Cole) serve as efflux pumps. In essence, the transporters work in concert to regulate intracellular drug levels. The transporters are expressed in tissue important for absorption (e.g. lung and gut) and metabolism (e.g. liver) of xenobiotics (Leslie et al.). In many cases, the ABC transporters also have a barrier function that regulates xenobiotic entry into sanctuary sites such as the brain or the blood - placenta barrier. Although both transporter types have critical roles in absorption and distribution of drugs, the ABC transporters have been the most studied. Of importance in drug metabolism are: (1) the multiple drug resistance gene (ABCB1) family (Yoshikawa et al.); (2) the eight member multiple drug resistance associated protein (ABCC1) family, and (3) the breast cancer resistance protein (ABCG1) family.

The multi-drug resistance family (ABCB1) is expressed in many normal tissues and has a role in the absorption and cellular excretion of toxic metabolites into bile and the intestinal lumen. Although 50 SNPs in the ABCB1 gene have been reported in different ethnic groups (Li et al.), only three (C3435T, C3435CC, and G2677T), have been implicated in drug resistance. C3435T, which is present in 24% of Caucasians, has been associated with increased plasma concentrations of digoxin (Sakaeda, Nakamura and Okumura). ABCB1 SNPs upregulating the efflux transporter, which is the receptor for corticosteroids, also have been associated inflammatory bowel disease (Farrell et al.).

The ABCC1 family (ABCC1-7 and 10), which confers resistance to nucleotide analogs, is usually associated with antiviral medication treatment failures. ABCC1 (MRP1), ABCC2 (MRP2) and ABCC3 (MRP3) are all able to facilitate the efflux of glucuronide and sulfate conjugates and endogenous molecules (Bai et al.). The ABCC2 transporter, which has sixteen SNPs, is the major efflux pump for HIV protease inhibitors such as saquinavir, zidovudine and zalcitabine (Huisman et al.). ABCC4 over expression is associated with high-level resistance to the nucleoside analogues 9-(2-phosphonylmethoxyethyl) adenine, azidothymidine (Borst et al.) and irinotecan/CPT-11 (Tian et al.) and is often used as a prognostic marker for aggressive tumors such as neuroblastoma (Norris et al.).

The ATP-binding cassette, subfamily G (ABCG family) has five members, ABCG1, ABCG2, ABCG4, ABCG5, and ABCG8, that act as efflux pumps (Kusuhara and Sugiyama). Cancer chemotherapy treatment failures are often associated with enhanced activity of breast cancer resistance protein (ABCG1) transporters on the surface of cancer cells. Substrates for the ABCG1 transporters include 7-ethyl-10-hydroxycamptothecin, topotecan, mitoxantrone, and flavopiridol (Sugimoto et al.). Nine mutant ABCG1 SNPs have been identified. In some instances, aberrations in the ABCG1 gene may be beneficial. Polymorphisms that prevent transporter production and expression (Sugimoto et al.) increase the amount of drug reaching the molecular target and increase efficacy (Yanase et al.; Zamber et al.). ABCG2 also confers resistance to anticancer drugs and plays a critical role in the pharmacokinetics of drugs in the clearance organs (Kusuhara and Sugiyama).

Phase I metabolic reactions and CYP450 enzymes

Phase I metabolic reactions are carried out via CYP 450 enzymes in the liver and small intestine (Wong, Seah and Lee). Over 270 CYP 450 families have been described but only three families (CYP1, CYP2 and CYP3) play major roles in drug metabolism (Frye). Approximately 50% of all clinically useful drugs are metabolized by CYP3A4. The remaining drugs are metabolized by CYP2D6 (20%), CYP2C9 (15%) and CYP2C19 (15%). Minor pathways of drug metabolism are catalyzed by CYP2E1, CYP1A2, CYP2A6, and unidentified P-450s (Frye). Because of a polygenic effect involving CYP3A5, the role of CYP3A4 SNPs in drug metabolism is unclear (Evans and McLeod). The 3A5 enzyme metabolizes many of the drugs that are also metabolized by the universally expressed CYP3A4. Hence, the net rate of metabolism often is the sum of polymorphic CYP3A4 and CYP3A5 (Evans and McLeod). More than 30 SNPs have been identified in the CYP3A4 gene. The most common variant, CYP3A4*1B has an allele frequency ranging from 0% (Chinese and Japanese) to 45% (African-Americans). However, studies have not linked CYP3A4*1B with alterations in CYP3A substrate metabolism (Lamba et al.). Since single-nucleotide polymorphisms in the CYP3A4 gene alter the activity of the enzyme for some substrates but not for others, these data should be considered preliminary in nature (Sata et al.). Linkage disequilibrium between CYP3A4*1B and CYP3A5*1 may be the critical factor in altered drug metabolism (Lamba et al.). Drugs that are normally metabolized by CYP3A4 and CYP3A5 are those likely to be used in the treatment of opportunistic infections in HIV patients (azole antifungals, macrolide antibiotics, and dapsone), or prevention of graft (cyclosporine and tacrolimus) rejection (Gibbons).

CYP2D6 genes are involved in both ADRs and TFs. In Caucasians, 7-10 percent of the population have a non-functional CYP2D6 gene (Egger et al.). Genetic polymorphism of CYP2D6 was originally discovered as a result of differences in the pharmacokinetics and therapeutic effects of substrate drugs such as codeine, dextromethorphan, metoprolol, and nortriptyline (Kroemer and Eichelbaum). In subjects with impaired gene function, severe adverse drug effects have been reported following administration of normal doses of anti-depressants and neuroleptics (Murphy et al.; Zackrisson et al.). Conversely, subjects with a defective CYP2D6 gene cannot bioactivate prodrugs such as donepezil, rivastigmine, galantamine, memantine and tamoxifen (Cacabelos).

Multiple human studies have demonstrated significant associations between CYP2C9 genotype and the metabolism of substrates such as warfarin, phenytoin and various sulfonylurea's, angiotensin II receptor blockers, and non-steroidal anti-inflammatory agents (Lee). CYP2C9*2 and CYP2C9*3 SNPs have been the most widely studied alleles. These alleles have been consistently associated with lower intrinsic clearance of drugs (Lee). Subjects carrying one or more variants may be a higher risk for ADRs. The risk increases significantly with warfarin and phenytoin that have an extremely narrow therapeutic index (Dervieux et al. Schwarz). In patients receiving warfarin, possession of two variant homozygous alleles appears to be associated with increased bleeding and a lower dose requirement (Daly and King). Phenytoin intoxication is also common in patients homozygous for the CYP2C9*3 allele (Brandolese et al.).

CYP2C19 variant alleles (CYP2C19*2 to CYP2C19*8 and CYP2C19*17) predict poor drug metabolizers (Desta et al.). Poor metabolizers of CYP2C19 represent approximately 3-5% of Caucasians and African Americans but are much higher (13-23%) in Orientals (Shilbayeh and Tutunji). The polymorphism affects metabolism of proton pump inhibitors such as omeprazole. There is little available information on the relationship of polymorphic CYP2C19 to UHs. In some instances, poor metabolism may be beneficial. Subjects with the variant CYP2C19 SNPs experience more effective acid suppression and better healing of duodenal and gastric ulcers during treatment with omeprazole and lansoprazole (Goldstein). Other substrates for the CYP2C19 are the anticonvulsant agent mephenytoin, the anxiolytic agent diazepam, certain antidepressants, and the antimalarial drug-proguanil.

Phase II metabolic reactions

Following the CYP450 introduction of functional groups in Phase I reactions, drug metabolites must be conjugated to other proteins to create water soluble complexes that can be excreted in bile or urine. Most Phase I metabolites are conjugated to glucuronide or glutathione. Glucuronidation is the major Phase II conjugation pathway in the body which requires the presence of UDP-glucuronosyltransferases (UGTs). These enzymes catalyze the glucuronidation of drug metabolites using oxygen, nitrogen or oxygen introduced or exposed in the Phase I reactions. Only a small number of UGTs catalyze the glucuronidation of thousands of compounds (Burchell). The UGT1A1*28 SNP has been identified in the promoter region of the gene and reduces promoter activity to 30% percent of normal. Most of the UGT1A SNPs are associated with the coding region of the gene. Untoward health effects often depend on the genotype. A heterozygous UGT1A6*2 phenotype results in reduced activity against phenolic compounds such as acetaminophen, salicylates and beta-blockers (Lampe et al.). Conversely, samples that were homozygous for UGT1A6*2 exhibited a high rate of glucuronidation relative to tissues with other genotypes (Nagar, Zalatoris and Blanchard). Prominent drugs that undergo glucuronidation are morphine, acetaminophen, chloramphenicol, cyclosporine A, tacrolimus and the irinotecan metabolite SN-38 (Ando, Hasegawa and Ando; Lankisch et al.).

The S-methyl transferases are another group of Phase II enzymes that are important in drug metabolism. The thiopurine S-methyltransferase (TPMT) gene is responsible for metabolism of 6-mercaptopurine and azathioprine. Genetic polymorphism in this gene has been correlated with high and low enzyme activity and clinical efficacy (Giacomini et al.; Seki, Tanaka and Nakamura). Rapid, clinically acceptable tests for TPMT polymorphisms have been developed and are widely used in clinical medicine (Giacomini et al.).

Glutathione (GSH) is the most abundant low-molecular-weight thiol in the body, and GSH/glutathione disulfide is the major redox couple in mammalian cells. Metabolites are coupled to reduced glutathione by glutathione S transferases. Four families of glutathione S transferases (alpha, mu, pi and theta) have been described (Mannervik et al.). SNPs in the pi, mu and alpha families usually produce non-functional or reduced function enzymes (Lida et al.). Some glutathione S transferases SNPs in the mu family appear to be protective. Low expression of the GSTM3*B variant may be protective against cisplatin ototoxicity (Peters et al.).

Glucose 6 phosphate dehydrogenase deficiency

Glutathione is maintained in a reduced state by the reduction of oxidized glutathione (GSSG) using NADPH as a cofactor. The glucose-6-phosphate dehydrogenase (G6PD) enzyme supplies the hydrogen to convert NADP to NADPH in the glutathione reduction pathway. Approximately 400 million people have partial or total deficiency in G6PD making it the most common X-linked enzyme deficiency in the world (Fujii). Over 130 G6PD variants have been reported (Luzzatto and Notaro) but only a few alter the synthesis or vary the enzymatic activity of G6PD. The "A" variant of G6PD possesses 85% of normal enzyme activity. Other SNPs (Med and A-) reduce the enzyme activity to 10-15 % of normal (Beutler; Ruwende et al.). Eleven percent of African American males in the United States have defective G6PD genes and increased risk for ADRs after administration of anti-malarial medications, sulfonamides, anti-itching drugs and dapsone (Fujii et al.). Deficiency of G6PD is associated with chronic and drug or infection-induced hemolytic anemia (Gervais and Prieur).

Summary

Pharmacogenomics has identified SNPs involved in drug metabolism. Accumulating data suggest that select SNPs (e.g. CYP2C9*2 and CYP2C9*3 SNPs in warfarin metabolizing genes) may have value in identifying persons at risk for UHEs. However, there is little information

concerning overlapping or redundant substrates for most CYP450 enzymes, and polygenetic effects in large populations. Until these issues are resolved, the clinical utility of SNPs in risk determination is clouded.

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