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Pharmacogenomics-Guided Approaches to Avoiding Adverse Drug Reactions

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Abstract

Adverse drug reactions (ADRs) are one of the major causes of patient morbidity and mortality. Pharmacogenomics is the study of how individual response to drugs is affected by genetic mutations at the genome level. There is clinical evidence that polymorphisms in genes encoding drug-metabolizing enzymes, drug transporters and drug targets (e.g. receptors & enzymes) can lead to the occurrence of ADRs. In addition, mutations of certain genes can precipitate ADRs. Over the past years, genome-wide association studies (GWAS) have identified a number of common and rare variants that are associated with increased risk of ADRs. As affordable and reliable genetic testing tools become available to physicians, pharmacogenomics looks promising to facilitate individualization of drug therapy and as a result, this will maximize the therapeutic efficacy of drugs in patients while minimizing the occurrence of ADRs.

Keywords: Pharmacogenomics; Single nucleotide polymorphism; Adverse drug reaction

Adverse Drug Reactions (ADRs) as Public Health Problems

A major public health problem in medical care is the occurrence of ADRs. Any substance that is capable of producing a therapeutic effect can also give rise to unwanted ADRs. Pharmaceutical agents have been identified as one of the most common causes of adverse events, resulting in significant patient morbidity, mortality and excess medical care expenditures. The variability of drug response from patient-to-patient is a major problem in clinical practice and in drug development as it can result in therapeutic failure or adverse effects of drugs in individuals or subpopulations of patients. The incidence of severe or fatal ADRs has been extensively examined in hospital inpatients. A meta-analysis of 39 prospective studies from hospitals in the United States suggests that approximately 6.7% of hospitalized patients have serious ADRs and 0.32% of them have fatal reactions, and thus there are probably more than 2,216,000 serious ADRs in hospitalized patients, causing over 106,000 per year in the US [1]. This figure appoints ADRs between the 4th and 6th leading causes of death in patients. ADRs were found to be the 7th most common cause of death in Sweden [2]. China's National Center for ADR Monitoring received 692,904 reports of adverse reaction cases in 2010. Also, it is estimated that over 350,000 ADRs occur in US nursing homes per year. In 2004, adverse drug events were noted in over 1.2 million hospital stays in the US, about 3.1% of all stays. In a study with 18,820 admissions to two National Health Service hospitals in the UK, 6.5% of patient admissions were due to ADRs [3]. The exact number of ADRs is uncertain and is limited by methodological limitations. One estimate of the cost of drug-related morbidity and mortality is $136 billion annually in the US.

WHO's definition of an ADR (1972) is "a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function". Furthermore, an ADR can also be defined as "an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen or withdrawal of the product".

ADRs can differ extensively in their clinical presentation and severity. It is important to include all drug-related diseases in the differential diagnosis in all patients presenting with new symptoms as ADRs can occur in any organ system and can mimic any disease process. Although the majority of ADRs are mild and do not require special therapy, there is a significant percentage that can be serious and fatal. The International Conference on Harmonisation has defined a serious ADR as any untoward medical occurrence that at any dose: results in death, is life-threatening, requires hospital admission or prolongation of stay in hospital, results in persistent or great disability, incapacity, or both, and also, is a congenital anomaly, birth defect, or both.

There have been many attempts to classify ADRs. The simplest has been to divide ADRs into two major categories: type A ('augmented') and type B ('bizarre'). Type A reactions are considered to be common, predictable and can occur in any individual. In contrast, type B reactions are uncommon, unpredictable and only occur in susceptible individuals. Type A reactions occur more frequently and has been reported to affect 25-45% of patients. These reactions are predictable from the known pharmacological actions of the drug, they are dose related and may be avoided and/or foreseen. On the other hand, type B reactions or idiosyncratic drug reactions cannot be justified on the basis of the drug's pharmacological actions and show no apparent dose-response relationship in susceptible individuals. Furthermore, type B reactions usually remain undiscovered until the drug has been marketed and are associated with a high mortality. In addition, two further types of reactions were added, reactions relating to both dose and time and delayed reactions. Consequently, these were labelled type C ('continuing') and D ('delayed') reactions. Moreover, type E reactions ('end of use') are associated with the withdrawal of a medicine. In recent

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years, the alphabetical categories havebeen extended even further: type F (failure), type G (genetic/genomic), and type H (hypersensitivity) reactions.

Genetic Polymorphisms of Genes are Associated With the Occurrence of ADRs

Although a proportion of ADRs is considered to be non-preventable, recent developments suggest these ADRs can be avoided through individualization of drug therapies based on genetic information, an application known as pharmacogenetics/pharmacogenomics. Pharmacogenetics was introduced in the 1950s after some researchers noticed that some ADRs could be linked to genetically determined variations in enzyme activity. The first example of an adverse reaction with a pharmacogenetic basis was illustrated in Southern Italy in 510 B.C. by Pythagoras, who reported that ingestion of fava beans can be harmful to some, but not all, individuals, leading to red cell hemolysis. Another example of hemolysis was described with primaquine, an antimalarial agent, in 1956, and was recognised as being caused by a deficiency of glucose-6-phosphate dehydrogenase. Also in the 1950s, the occurrence of prolonged apnoea was observed after the treatment of suxamethonium (a nicotinic acetylcholine receptor antagonist used to induce muscle relaxation and short-term paralysis) in patients with an inherited deficiency of butyrylcholinesterase. In the 1960s, it was found that peripheral neuropathy, which was associated with the administration of isoniazid used for the treatment of tuberculosis, was due to the inherited deficiency of N-acetylation of the drug in the so-called slow acetylators. ADRs such as nausea, diplopia, and blurred vision after ingestion of the antiarrhythmic and oxytocic drug, sparteine, or the incapacitating orthostatic hypotension after the use of the antihypertensive agent, debrisoquine, have led to the discovery of the genetic polymorphism of the drug-metabolising enzyme, cytochrome P450 2D6 (CYP2D6) [4,5].

In a systemic review attempting to quantitatively address the role of polymorphisms in cytochrome P450 genes in predisposing to ADRs, it was found that of the 27 drugs most frequently cited in ADR studies, 59% were metabolized by at least one CYP with a variant allele associated with reduced enzyme activity, compared with 7% to 22% of the randomly selected drugs [6]. To date, we have accumulated a number of clinical data that polymorphisms of *CYP2C9, CYP2C19,* and *CYP2D6* are associated with an increased risk of ADRs [7]. For example, there were more individuals with the *CYP2C9*1/*3* genotype among Korean patients with skin reactions to phenytoin compared with non-exposed controls. The *CYP2C9*2* or **3* genotype was associated with increased risk of a gastric bleeding episode after NSAID dosing with an odds ratio of 2.6 (e.g. celecoxib, diclofenac, ibuprofen, indomethacin, lornoxicam, piroxicam, or naproxen) [8]. In addition, 82% of patients who were wild-type for *CYP2C19* and carried only one functional *CYP2D6* allele experiences significant toxicities when treated with amitriptyline at 75 mg twice daily [9]. Poor metabolizers of CYP2D6 may experience greater exposure to tamoxifen's adverse effects including venous thrombosis and endometrial cancer [10].

Polymorphisms of the Phase II enzyme *N*-acetyltransferase-2 (NAT2) have been found to be related to ADRs upon treatment with isoniazid, dapsone, and sulphoniazides. Studies have shown an increased risk of renotoxicity in response to isoniazid in poor metabolizers for NAT2 including increased hypersensitivity to therapy with sulphonamines as well as hydralazine-induced toxicity [11]. TPMT works as a cytosolic enzyme that catalyzes the inactivated *S*-methylation of thiopurine drugs such as 6-mercaptopurine which is extensively used in the treatment of acute lymphoblastic leukemia. This enzyme is encoded by the *TPMT* gene which is located on chromosome 6p22, also consisting of 10 exons and 9 introns spanning 34 kb. The autosomal co-dominant inheritance of the *TPMT* genetic polymorphisms has been linked to the loss of erythrocyte TPMT activity and also, the severe hematopoietic toxicity of thiopurines [12]. As a result, individuals who have reduced TPMT activity are exposed to highly elevated levels of active drug in hematopoietic tissues after given normal doses of 6-mercaptopurine. Consequently, very high concentrations of cytotoxic thioguanine nucleotide are produced, predisposing the individuals to severe hematopoietic toxicity.

UDP-glucuronosyltransferase (UGT1A1) is a microsomal phase II drug-metabolizing enzymeresponsible for catalyzing the detoxification of SN-38 formed from irinotecan to a polar inactive SN-38 glucuronide that is consequently excreted in the bile. This protein is encoded by the *UGT1A* gene on chromosome 2q37. Patients carrying *UGT1A1*28* are subject to increased risks of dose-limiting toxic effects of irinotecan such as severe diarrhea, and neutropenia [13].

Drug responses are exerted through interactions between medications and membrane receptors (about 50% of drugs), enzymes (about 30%), or ion channels (about 5%). Polymorphisms in the genes which encode these proteins may cause a variation in the drug response, effecting the drug efficacy and toxicity. For example, the β_2-adrenergic receptor has been well studied and some of its mutations such as the Arg→Gly at amino acid 16 are major determinants of the β_2-agonist bronchodilator response [14]. Additionally, substitution of three key amino acids can alter the function of the receptor considerably. Enhanced agonist-promoted down-regulation has been seen in mutant R16G, on the other hand, mutant Q27E is resistant to down-regulation and also, mutant T164I displays altered coupling to adenylyl cyclase. Further studies have supported the fact that polymorphic forms of the β_2-adrenergic receptor has a contributing role in promoting asthmatic phenotypes, creating bronchial hyperactivity and manipulating the response to acute or chronic β-agonist therapy.

Dihydropyrimidine dehydrogenase (DPD) is a rate-limiting enzyme involved in the detoxification of 5-fluorouracil, an important anticancer agent. Studies have shown that a heritable defect in DPD can result in 5-fluorouracil-related severe toxicity such as myelotoxicity, gastrointestinal toxicity and neurotoxicity in cancer patients. Methylenetetrahydrofolate reductase (MRHFR) is responsible for the metabolism of folate, and this has a major role in nucleotide synthesis. There has been an association of mutations in *MRHFR* and an increased risk of developing adverse reactions in patients taking methotrexate [15]. Many polymorphisms have been described in *MFHFR*, however, those which cause a reduction in enzyme activity are the C677T and A1298C polymorphisms. The C677T polymorphism results an Ala for Val substitution in the enzyme with a reduce activity. Furthermore, this polymorphism can produce increased plasma homocysteine levels, which has been correlated to the pathogenesis of various adverse effects such as, gastrointestinal symptoms. Recent studies have led to the understanding that overall methotrexate's toxicity in patients with rheumatoid arthritis, which consist of increases in transminases, stomatitis, nausea, hair loss and rash, was more widespread in patients having the T-allele at position 677 of the MTHFR gene [16].

Genetic Mutations of Genes that Precipitate ADRs

Human leukocyte antigen (HLA) has been displayed as a good example of an association being the higher risk of hydralazine-induced lupus in patients who are HLA-DR4 positive. In addition, hydralazine-induced lupus provides an early example of the polygenic nature of the predisposition to ADRs. This is because individuals who are both slow acetylators and HLA DR4-positive have a higher risk compared to those with only one risk factor [17]. Abacavir is a potent HIV-1 reverse

potent HIV-1 reverse transcriptase inhibitor used in the treatment of HIV. However, its use is complicated due to the potential occurrence of life-threatening hypersensitivity reactions which occur in 5% of patients [18]. The hypersensitivity symptoms will aggravate with continued therapy, however they generally improve with 24 hr of discontinuation of therapy. After a widespread investigation of the major histocompatibility complex, it was discovered a strong association lies between abacavir hypersensitivity and the haplotype comprising *HLA-B*5701, HLA-DR7*, and *HLA-DQ3* [19].

With the application of advanced genetic testing technology [e.g. genome-wide association study (GWAS)], there are increased reports on the identification of common or rare genetic mutations that are associated with and often precipitate ADRs (see Section 6 below). For instance, individuals carrying the SNPs in *RBMS3, IGFBP7* and *ABCC4* were more likely to develop bisphosphonate-related osteonecrosis of the jaw [20]. Children positive for *L461L* within the *SLC28A3* gene showed a higher risk of developing anthracycline-induced cardiotoxicity [21]. In addition, depressive patients harboring with SNPs of *SACM1L, MAGI2, DTWD1, WDFY4* and *CHL1* had a higher risk of experiencing antidepressant-induced side effects [22].

Genome-wide Association Study (GWAS) Allows to Identify More Genetic Variants Associated with the Occurrence of ADRs

The availability of the large number of genome-wide SNPs and high-throughput genotyping technologies in recent years has made it possible to identify the genetic variants conferring significant risk to ADRs. Due to the open nature of this strategy, the causal variants can be potentially identified without *a priori* hypothesis. The paradigm of pharmacogenetic studies using typical candidate gene-based approach has thereby shifted to phamacogenomics level with high density genome-wide SNP markers. Although this approach is often limited by the difficulty in collecting a large number of cases and controls, many GWAS have been conducted thus far and a number of loci significantly associated with drug-induced sever toxicities have been successfully identified [23,24]. Major findings include the identification of a few HLA loci for the hepatotoxicities induced by antibiotics (*HLA-B*5701*) and carbamazepine-induced hypersensitivity and skin reactions (*HLA-A*3101*) [25], and a *SLCO1B1* polymorphism and simvastatin-induced myopathy [26]. Most of these studies have been independently confirmed with additional samples [24]. Notably, the majority of the risk alleles identified among these studies have a relatively large effect size, e.g. the odds ratio for the allele of *HLA-B*5701* associated with flucloxacillin-induced liver injury is 45 [27], which is in contrast to the majority of GWAS findings for complex diseases and other traits, suggesting a great potential for clinical translation, e.g. genotype-based selection of drugs or adjustment for drug dosage. In addition, a few other GWAS have been recently published including an association between lamotrigine-induced skin injury [28] and an *ADAM22* polymorphism, bisphophate-induced osteonecrosis of the jaw and the *CYP2C8*, SNP rs1934951 [29,30], as well as *TCL1A*SNPs and musculoskeletal adverse events induced by the aromatase inhibitors such as anastrozole andexemestane in women with early breast cancer [31]. These studies warrant further validation in other populations.

Pharmacogenomics-guided Approach to Avoiding ADRs

The main goal of genetic testing is to provide the individual with maximum efficacy to drug response and while doing so, reduce the possibility of experiencing an ADR. For a laboratory test to be clinically useful, it should provide information that is relevant to the therapeutic decision. Relevant information includes the dose of a certain drug and also a potential alternative as contraindications may be present or the poor response due to a particular genetic polymorphism. It is likely that pharmacogenetic laboratory information can allocate patients into several groups, such as, ultra-rapid metabolisers, normal metabolisers, and also poor metabolisers.

The FDA approved the first genotype test intended to be used by physicians to help guide the selection of drugs metabolized by the CYPs. The AmpliChip CYP450 test is a DNA microarray that can detect several polymorphisms such as the 29 polymorphisms of *CYP2D6* and the two polymorphisms of *CYP2C19* using a blood sample. Thereafter, more pharmacogenetic tests have been approved by FDA. These include *UGT1A1* genotyping for irinotecan, *KRAS* mutations for cetuximab, and HER-2 tests for herceptin. Although there is evidence supporting the link between adverse effects and polymorphisms, more clinical trials are needed to determine whether genotyping is cost-effective and improves clinical outcomes.

Genomic information opens a pathway allowing a more precise prediction of an individual's drug response and hence a more suitable selection of drugs and drug dosage and hence an individualised drug therapy. Consequently this will result in the best possible therapeutic response while avoiding therapeutic failures. Finally, as ADRs represent a major public health problem, genetic testing will help to predict the risk of experiencing ADRs in patients on pharmacotherapy, thereby reducing the incidence of toxicity.

With the knowledge of pharmacogenetics, there are many approaches which can be taken to avoid ADRs. Initially, the risk versus benefit ratio should be calculated and only when the benefits outweigh the risks of taking a certain medication should therapy be initiated. Once therapy has started, the patient should be monitored on the therapeutic effectiveness on the medication and only if the therapeutic effect is established, should the treatment continue. On the other hand, it is crucial to be aware of the toxicities which may develop for that particular medication and furthermore be alert for the signs of toxicity. It is important that patients avoid polypharmacy as this can lead to contraindications and thus further possible complications. Before prescribing any drugs, physicians should be aware of the individual's history, including drug use history, family history and allergies. Furthermore, it is vital to take into account the patient's age, body weight and health status such as renal function. Following these approaches will lead to a more effective and safer therapy for the patient, thus, an individualized pharmacotherapy.

There are two general goals in the study of pharmacogenetics and these include, the ability to predict those patients at high risk of toxicity (and hence a lower dose or change in therapy would be advised) and the ability to predict those patients who are more likely to obtain the desired therapeutic efficacy from the drug. Through prediction of how certain patients will respond to a drug, it is likely to avoid the unwanted ADRs.

Conclusions and Future Perspectives

In conclusion, adverse drug reactions are a major problem in society and are costing the medical industry billions of dollars every year. Pharmacogenetics is still in its early stages in regards to clinical practice; however positive prospective lie ahead as this may be the new era of individualized drug therapy. Individualized drug therapy allows the individual to get the optimal therapeutic response of the drug while minimizing the possibility of acquiring an ADR. This is achieved through consideration of all contributing factors including environmental factors and genetic variability in the particular individual. This report

has analyzed some of the important genetic variations in different individuals; including genetic polymorphismsof drug-metabolizing enzymes, drug transports and drug receptors. These variations have been linked to certain drugs and hence the adverse effects which may occur. However, many drugs have complex metabolic pathways therefore multiple variant alleles may be responsible for ADRs.

An important goal for the next decade is to advance the study of pharmacogenetics to a point where a significant amount of drugs are individualized for patients based on their genetic information. Mutant alleles at a single gene locus are best studied individual risk factors for ADRs. Awareness of inherited variations of drug responsiveness, which remain constant throughout life, can lead to possible dose adjustments on the basis of the patient's genetic makeup and are also likely to prevent ADRs.

There are numerous factors which contribute to the occurrence of ADRs and variation in drug responses in different individuals. Some of these factors include patient age, sex, body weight, nutrition, organ function, infections and co-medications. Lifestyle variables such as smoking and alcohol consumption are also potential risk factors. Also, poor prescribing behaviour, for example, prescribing inappropriate doses in the presence of a contraindication or co-prescribing two drugs with a potential interaction may also result in an ADR. However, when these "environmental" factors are removed, a substantial proportion of ADRs remain present due to a genetic predisposition. It has become evident in recent years that genetic factors may also significantly alter drug responses or increase the risk for ADRs. Most drug effects are established by the inter-play of several gene products that influence the pharmacokinetics and pharmacodynamics of medications, including inherited differences in drug targets (e.g. receptors) and drug dispositions (e.g. metabolizing enzymes and transporters). Some genes can regulate the body's response to drug therapy via the immune system or other pathways, thereby increasing the risk of ADRs in patients carrying certain mutations. Furthermore, interactions between environment and genetic factors can also predispose to the development of an ADR.

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