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Extended Abstract

Pharmacogenomics-guided approach to minimize adverse drug reactions

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Abstract

Adverse drug reactions (ADRs) are one of the major causes of patient morbidity and mortality. Pharmacogenetics is the study of how the genetic variations affect drug response in individual patients, while pharmacogenomics emphasizes the identification of the network of genes that govern drug response in individual patients using genome-wide approaches. Numerous genes, in particular those encoding drug metabolizing enzymes, drug transporters and drug targets, have been identified to affect drug response and ADRs. In the past decade, my laboratory has investigated the impact of polymorphisms of a number of important genes including CYP2B6, CYP2C9, ApoE, PXR/NR1I2, UGT1A1, GSTM1, GSTT1, GSTP1, TPMT, etc. on drug clearance, response, or ADRs. Mutations of these genes can significantly alter drug clearance, response or ADRs in different ethnic groups. 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

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

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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