PHARMACOGENETICS – THE FUTURE OF THE DRUG THERAPY

Natasa Djordjevic and Slobodan Jankovic

Individual variation in response to drugs is an important clinical problem, which ranges from failure to respond to a drug to adverse drug reactions. Medical therapy still aims at the broadest patient population that might possibly benefit from it, relying on statistical analysis of this population's response for predicting therapeutic outcome. Yet, certain percentage of patients will obtain no benefit from a given drug, or will experience toxicity. Pharmacogenetics, which deals with the genetic basis underlying variable drug response, offers the potential of individualizing drug therapy, and through optimizing efficacy and minimizing toxicity it increases the possibility for a wide range of diseases to be cured and controlled. *Acta Medica Medianae 2007;46(2):56-60.*

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Department of Pharmacology and Toxicology, Faculty of Medicine in Kragujevac

Correspodence to: Natasa Djordjevic
Department of Pharmacology and Toxicology, Faculty of Medicine
34000 Kragujevac, Serbia
Phone: 027/324-000
E-mail: natashadj2002@yahoo.com

The definition

Individual variation in response to drugs is an important clinical problem, which ranges from failure to respond to a drug to adverse drug reactions and drug-drug interactions when several drugs are taken concomitantly (1). Many non-genetic factors (including age, organ function and nature of the disease) influence the effects of medications, but it is estimated that genetics can account for 20 to 95% of variability in drug disposition and effects (2). The genetic constitution of an individual, as extremely relevant factor for both efficacy and safety of a given drug regimen (3), makes the central topic of pharmacogenetics, as a special scientific discipline arised from the confluence of genetics, biochemistry, and pharmacology (4).

Pharmacogenetics has been defined as the science of pharmacological response and its modification by hereditary influence; the subjects of interest relate both to efficacy (therapeutic effectiveness) and toxicity (production of side effects or unwanted effects) (5). Dealing with the genetic basis which underlies variable drug response in individual patients, it develops an individualized approach to the therapy, where optimally effective drugs are matched to a patient's unique genetic profile (4). Pharmacogenetics provides insight into the molecular level of drug function and, as a consequence, offers the potential of individualized drug therapy (6). Thus it can help in optimizing drug efficacy and minimizing adverse drug reactions (7).

The terms "pharmacogenomics" and "pharmacogenetics" can be considered to be almost synonymous (8), but pharmacogenomics can best be defined as the application of whole-genome technologies for the prediction of the sensitivity or resistance of an individual's disease to a single drug or group of drugs (9).

Historical perspective

It is now well-known that all humans are remarkably similar, in fact 99.9% identical, at the level of their deoxyribonucleic acid sequence (10). The field of genetics thus has evolved to include the study of inter-individual genomic variation, focusing on the 0.1% of our genome that makes each individual genetically unique (11). In 1902, British physician and pioneer in medical genetics, Sir Archibald Garrod, studying alcaptonuria in humans, published a paper about "inborn errors of metabolism" (12). Pharmacogenetics as a science was born in the 1950s when it was reported that several therapeutic accidents could be hereditary (13), meaning that they can be induced by genetic variations of enzyme activity. The concept of pharmacogenetics originated from the clinical observation of patients with very high or very low plasma or urinary drug concentrations, which indicated exceptional phenotypes (14), and one of the first

described was haemolysis after antimalarial therapy occurring in persons who expressed deficiency in glucose-6-phosphate-dehydrogenase (15). Those discoveries marked the beginning of a pharmacogenetics as a new clinical discipline, which now has applications in many fields, including drug development and therapeutic dosing guidance (16).

Over the last 50 years, a number of events led the research toward the identification of differences in drug response of individual patients (6): in 1957 genetic traits and enzyme deficiencies were described as causes for idiosyncratic drug reactions, in 1959 Friedrich Vogel coined the term "pharmacogenetic", defining it as "clinically important hereditary variations", in 1962 first book about pharmacogenetics was published by Werner Kalow, in 1977 the polymorphic hydroxylation of debrisoquine in men was described and in 1988 common genetic defect in the CYP2D6 gene in humans deficient in debrisoquine metabolism was characterized. In 2003, 50 years after the famous publication on DNA structure by James Watson and Francis Crick (17), "The Human Genome Project" was completed, which provided the new opportunities in using genetic information for individualizing drug therapy (18).

Pharmacogenetics polymorphism

The term pharmacogenetic polymorphism defines a monogenetic trait, caused by the presence of more than one allele at the same locus and more than one phenotype in the same population in regard to drug interaction with the organism, with the frequency of the rarest allele of more than 1% (19). DNA sequence variations may occur as insertions or deletions of nucleotides, differences in the copy number of repeated sequences or SNPs - Single Nucleotid Polymorphisms (20, 21). If the mutations occur in proteins that are drug targets or drug-metabolizing enzymes, or in proteins that are involved in drug transport mechanisms, they can affect drug efficacy and safety (15).

Genetic polymorphism in drug metabolism, according to their ability to perform a certain drug biotransformation reaction, defines three distinct populations: poor metabolizers (PM), extensive metabolizers (EM) and ultrarapid metabolizers (UM). The PM phenotype is monogenically inherited as an autosomal recessive trait and it is due to complete absence or marked decrease in the amount and/or activity of the enzyme. The poor metabolizers are unable to metabolize drug to the full extent, so the clinical consequences of the PM phenotype are the side effects and toxicity after administration of an active drug; if the metabolite has the therapeutic effect, a therapeutic failure may be expected after giving the prodrug (22). On the other hand, the UM phenotype is due to the presence of duplicated genes resulting in expression of increased amount of enzyme. The clinical consequence of the UM phenotype is the inability to reach therapeutic plasma-concentrations after administration of an active drug in a usual dose,

which results in a therapeutic failure; administration of a prodrug may cause toxicity (23). The EM phenotype is the most common and it represents the norm for standard dosing practi-ces in drug administration. Their metabolizing capacity depends on whether they are homozigous or heterozigous for the active form of the gene producing the drug metabolizing enzyme (24).

Clinical applications

Understanding of the genetic variations and their influence on individual response to drug therapy increases the possibility for a wide range of diseases to be cured and controlled. Many different drugs can illustrate the clinical importance of pharmacogenetics.

There was significant advance in treating elevated blood pressure over the last decades, yet hypertension continues to be a major public health problem (25). Despite the great number of antihypertensive drugs that are available, in between half and two-thirds of treated hypertensive patients blood pressure control stays suboptimal, while adverse effects represent approximately 80% of the causes for the discontinuity of the antihypertensive therapy (26,27). One of the drugs frequently used for lowering blood pressure in patients with hypertension is metoprolol. It is a β1-blocking drug extensively metabolized in the liver, mostly under control of polymorphic drug-metabolizing enzyme cytochrome P450 2D6 (CYP2D6), a major determinant of interindividual differences in metoprolol plasma clearance (28, 29). It has been found that poor metabolizers (PM) exhibit 3- to 10-fold higher plasma concentrations after administration of metoprolol than extensive metabolizers (EM), while ultrarapid metabolizers (UM) achieve metoprolol concentrations that are half those observed in EMs (30), which shows a strong gene-concentration relationship (29). In terms of a gene-effect relationship, metoprolol has been reported to produce a more intense and prolonged β-blockade in PM than in EM subjects (31). Therefore, while PMs would require only once-daily treatment with metoprolol 100 mg for effective blood pressure control, EMs would usually require twice-daily treatment with metoprolol 100 mg (32). Furthermore, since the mRNA for CYPD6 has been found to be predominantly expressed in the right ventricle (33), the genetic polymorphism of CYP2D6 can be considered as an important risk factor in treating cardiovascular patients with metoprolol and the genotyping should be used to estimate at least the initial dose required (34).

The treatment of epilepsy offers another opportunity for the application of pharmacogenetics into clinical practice, because of the wide variety of individual responses to antiepileptic drugs that leads to adverse drug reaction (35) or inadequate seizure control (36) in half of the patients currently treated with antiepileptics (37, 38). One of the important and effective antiepileptic drugs is phenytoin, widely prescribed throughout the world, but narrow therapeutic

index of the drug makes it difficult, time consuming and expensive for finding out the correct dose (39, 40). Phenytoin is almost completely metabolized in the liver, and many studies clearly indicate that the main enzyme involved in phenytoin clearance is CYP2C9, which is responsible for up to 90% of drug inactivation (40-42). Yet, the evidence about contribution of CYP2C19, which increases with increase in phenytoin concentrations, suggest that CYP2C19 might be important when CYP2C9 is saturated (42). The activity of CYP2C9 varies up to 10-fold in vivo, with one in every 500 individuals exhibits deficient activity of this enzyme (43), while several genetic variants of CYP2C19 that have been reported cause the poor metabolizer phenotype in approximately 10% of Caucasians (44). Several studies of phenytoin have shown that variations in the genes CYP2C9 and CYP2C19 correlate with the maximum dose of drug needed by patients to control their seizures: patients who were poor metabolisers for these genes needed up to 75% lower dose of phenytoin than the extensive metabolisers to achieve the therapeutic concentrations of the drug in serum (45-47). Because of the narrow therapeutic index of phenytoin, minimum toxic serum concentration can be easily exceeded even with the moderate doses that are given during induction of therapy; thus it becomes clear that genotyping for CYP2C9 and CYP2C19 allelic variants could, together with serum drug concentration monitoring, facilitate and accelerate a proper phenytoin induction and decrease the risk of intoxications, contributing to the individualization and optimalization of the therapy (46).

It is estimated that 15% of the population will develop depression during their lifetime, and that the prevalence is 5% (48). Depression is a severe disorder that needs to be treated, yet about 30–50% of patients will not respond sufficiently to the therapy, regardless of the initial choice of standard psychiatric medication (49,50). In the disposition of tricyclic antidepressant nortriptyline, widely used in the treatment of patients with depression, noticeable inter-individual variability has been well- documented (51). Plasma concentrations of this drug, with metabolism up to 80% mediated by the highly polymorphic enzyme CYP2D6 (29), have been shown to vary in relation to CYP2D6 genotype (51), and many studies supported the existence of a concentration-effect relationship for the antidepressant action (52). There are several case reports documenting toxicity due to elevated nortriptyline concentrations in PMs lacking CYP2D6 activity, but also treatment failures in UMs with multiduplicated functional gene (48): individual response thus can vary remarkably, ranging between experiencing adverse effects early in the course of therapy (53) and not being able to reach therapeutic plasma concentrations even with doses of drug much higher than usual (54). Although only 20% of ultrarapid metabolizers can be predicted from the results of genotyping, testing for a limited set of CYP2D6

alleles may distinguish with almost 100% accuracy the vast majority of Caucasian individuals lacking CYP2D6 activity (53), therefore prior knowledge of the CYP2D6 genotype have potential to improve the choice of initial dosage of nortriptyline to the individual patient (51).

Interindividual variability in response to drug therapy is the rule, not the exception, for almost all medications (55). Having that in mind, the need for translation of pharmacogenetics from laboratories to the bedside can be easily understood.

The goals

Medicine of the third millennium still targets therapy to the broadest patient population that might possibly benefit from it, and it relies on statistical analysis of this population's response for predicting therapeutic outcome in individual patients. However, any given drug can be therapeutic in some individuals but ineffective in others, and some individuals can experience adverse drug effects while others can be unaffected. Recognition of those inter-individual differences in drug response is an essential step towards optimizing therapy (4).

Currently there are two main treatment approaches in the pharmacological management of disease: trial and error approach and per protocol approach. The first is employed for drug treatment of diseases such as hypertension, diabetes and depression, where several drugs are considered as a reasonable first line therapy: trial and error approach means finding the drug(s) that is most effective in a given patient, and can often take months to accomplish. When the treatment for a given disease is essentially the same for everyone with that diagnosis, e.g. most cancers, heart failure and myocardial infarction, per protocol approach is mainly used. Whatever the approach is, a certain percentage of patients will obtain no benefit from a given drug, or will experience serious adverse effects. The clinical application of pharmacogenetics, thus, has two main goals: to predict the patients at high risk of toxicity (and in whom a lower dose or a different drug should be administered) and to indicate those who are most likely to obtain the desired therapeutic effect from the drug (56). Pharmacogenetics is expected to improve, even to overturn, current approaches to drug treatment by reducing adverse reactions, increasing drug efficacy and refining prescribing practices (10).

It is now clear that virtually every pathway of drug metabolism will eventually be found to have genetic variation. However, the overall pharmacologic effects of medications, influenced by metabolism, but by apsorption, distribution, excretion and the drug target itself as well, are usually determined by the interplay of several genes encoding proteins involved in both pharmacokinetics and pharmacodynamics (15). Thus the field of pharmacogenetics, which began with a focus on drug metabolism and monogenetic traits, has been extended and nowadays covers

the full spectrum of drug disposition and the role of multiple genes (57, 58). Today there is a systematic search to identify functionally significant variations in DNA sequences in genes that influence the effects of various drugs (12). The potential benefits of increased understanding of pharma-cogenetic variation are choosing the right drug and adjusting dosage (59). The ultimate goal for the future is to develop individualized effective and safe therapies based on a predetermined individual genomic profile (60).

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FARMAKOGENETIKA – BUDUĆNOST MEDIKAMENTOZNE TERAPIJE

Nataša Đorđević i Slobodan Janković

Individualne varijacije u odgovoru na lekove važan su klinički problem i kreću se od potpunog odsustva reakcije na lek do pojave neželjenih reakcija. Medicina i dalje usmerava terapiju ka najširoj populaciji bolesnika koji od nje mogu imati koristi, oslanjajući se na statističke analize i predviđanju ishoda lečenja. Ipak, određeni broj bolesnika neće imati nikakve koristi od primenjene terapije ili će biti intoksicirani. Ispitujući genetsku osnovu koja uzrokuje individualne varijacije u odgovoru na lekove, farmakogenetika omogućava individualizaciju medikamentozne terapije, te postizanjem optimalne efikasnosti i smanjenjem pojave neželjenih efekata lekova povećava mogućnost kontrolisanja i lečenja velikog broja oboljenja. *Acta Medica Medianae 2007;46(2):56-60.*

Ključne reči: *farmakogenetika, genetski polimorfizam, metabolizam lekova, reakcija na lekove*