Pharmacogenetics in health-care practice

• Anke-Hilse Maitland-van der Zee, Olaf H. Klungel and Anthonius de Boer

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A.-H. Maitland-van der Zee (correspondence, e-mail: amaitland@sph.uth.tmc.edu): **O.H. Klungel, A. de Boer**: Department of Pharmacoepidemiology & Pharmacotherapy, Utrecht Institute of Pharmaceutical Sciences (UIPS), Utrecht University, Utrecht, The Netherlands, and Human Genetics Center, University of Texas Health Science Centre, Houston, Texas, USA

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Introduction

One of the most challenging areas of research in clinical pharmacology and pharmacoepidemiology is the attempt to understand why individuals respond differently to drug therapy. Problems with drug therapy can be divided into two main categories. The first problem is that drugs are not effective for all patients. If it is possible to predict the effectiveness of a drug in advance, this would save inconvenience for the patients who do not benefit from the drug; it would also save costs.

The other major problem in drug therapy is the occurrence of adverse events[1, 2]. Every year, more than two million hospitalized patients in the United States experience severe adverse drug reactions, even when drugs are appropriately prescribed and administered[2]. The cost of severe adverse drug reactions in individuals has been estimated to be in excess of US$4 billion in the United States alone[3]. In the Netherlands the costs of hospital admissions related to adverse drug reactions were estimated to be between US$158 and US$365 million.

The field of Pharmacogenetics is concerned with the extent to which variability in genetic make-up is responsible for the observed differences in therapeutic efficacy and adverse reactions among patients. The aim of pharmacogenetics is to shape individualised therapies using available medicines.

It is estimated that 47–61% of all protein-coding loci are polymorphic[4]. Thus the mutation of genes that may potentially affect drug response is a common biological phenomenon. The consequences for drug response will depend on the extent to which the function of the gene product is affected by the mutation. In addition to the magnitude of loss of function, the frequency with which the mutation occurs determines the clinical relevance of genetic variability. Principally, there are three routes by which genes can affect response to a drug.

Pharmacokinetic interaction

The first route is the pharmacokinetic one. Gene products relevant to the pharmacokinetics (biotransformation and excretion) of drugs comprise various enzyme systems (e.g., cytochrome P450 enzymes), ATP binding cassette (ABC) transporter proteins (proteins involved in the absorption, excretion and transport of drugs across bodily barriers, e.g., the blood– brain barrier), etc. There is ample evidence of the important role of different genotypes that code for these enzymes[5]. Changes in enzyme activity can cause a substantial variation in the amount of drug present in the body. For example, the cytochrome P450 2C9 enzyme is associated with the metabolism of phenytoin. It has been observed that the plasma level of phenytoin varies 16-fold among patients given the same dose of the drug[6]. Variation in the activity of these drug-metabolising enzymes results in variable pharmacokinetics: rapid metabolisers will be underdosed and poor metabolisers will be overdosed. When multiple drugs are administered to a patient, this variation may result in unpredictable drug–drug interactions[7]. Another example of a pharmacokinetic interaction is found with cytochrome P450 2D6. Subjects who are homozygous for the cytochrome P450 enzyme 2D6 (CYP2D6) null alleles exhibit a 'poor metaboliser' phenotype, which occurs in 3 to 10% of Caucasians[8]. Other genotypes for this enzyme (on chromosome 22) lead to phenotypes that can be classified as extensive or ultra rapid metabolisers. Cytochrome P450 2D6 is involved in the metabolism of many cardiovascular drugs and antipsychotics. Subjects with the 'poor metaboliser' phenotype have a higher risk of developing extrapyramidal side effects when they use classic antipsychotic drugs[9, 10]. In several psychiatric hospitals in the Netherlands patients are already routinely genotyped for this enzyme[9].

Another example of a pharmacokinetic interaction that is already used in practice can be found in cancer pharmacogenomics. A polymorphism in thiopurine methyltransferase (TPMT) results in altered degradation of 6-mercaptopurine. This genetic variant has significant clinical implications because patients without functional enzyme activity (relevant homozygous mutations in the TMPT gene (0.3% of the population[11])) experience extreme or fatal toxicity after administration of normal dosages of 6-mercaptopurine. It has been shown in children with acute lymphoblastic leukemia who have this mutation it has been shown that they can be successfully treated with a 10 to 15 times lower dosage[11, 12].

Pharmacodynamic interaction

The second route by which genes can affect drug responses is the pharmacodynamic one. Gene products expressed as drug targets, such as receptors and signal transduction modulators, are relevant to the pharmacodynamics of drugs. After entering the body each drug interacts with numerous proteins, such as carrier proteins, transporters and multiple types of receptors. These proteins determine the site of action and the pharmacological response. Thus, polymorphisms in genes encoding for drug targets may affect the response to a drug[13]. For example, polymorphisms in

the coding region and promotor of the serotonin receptor are associated with the beneficial effects of atypical antipsychotic drugs (e.g. clozapine)[14]. The evidence base for the use of these drugs is compelling, but a variety of reasons seem to prevent their use in greater numbers of eligible patients. The response to atypical antipsychotic drugs is variable (between 30 and 60% respond to clozapine) and treatment costs are higher than classic antipsychotics, because it is necessary to screen for effects on blood (counting white blood cells) before and during the use of clozapine. In a study by Arranz et al., a combination of six polymorphisms in neurotransmitter-receptor related genes resulted in 76.6% success in the prediction of clozapine response[14]. Although such results need confirmation in other settings, they can be implemented in a treatment protocol with a simple test to enhance the usefulness of clozapine in psychiatric treatment. There is also evidence that polymorphisms in the dopamine D4 receptor may explain some of the inter-individual variation seen in patient response to clozapine and other classes of antipsychotic medication[15].

Interaction with genes in the causal pathway of disease

Finally, there is a growing interest in genes that are in the causal pathway of diseases and are able to influence the drug response[4, 16]. A complicating factor is that most diseases have a polygenetic origin and that different genetic pathways may therefore operate in patients with the same phenotype. These genetic differences may also lead to different responses to drug treament.

An example is the factor-V Leiden mutation. The incidence of venous thrombosis among non-users of oral contraceptives is about 0.8 per 10000 person years. This risk increases to 5.7 per 10000 person years for carriers of the factor-V mutation. The risk increases to 3 per 10000 person years for women who use oral contraceptives. Among women who have both risk factors (carriers of factor-V Leiden who use oral contraception) the incidence becomes 28.5 per 10000 person years, so the joint effect of gene and exposure is about 3.2 times greater than the sum of their individual effects, and about 1.3 times greater than the product of their individual effects[17].

Thus, for carriers of the factor-V Leiden it may be better to use other methods of birth control than oral contraceptives.

Practical implications

The ethical, legal and social implications of population- based genotyping are still unresolved and much debated. It is important that distinctions are made between disease susceptibility gene polymorphisms which provide information about risks of diseases, and pharmacogenetic profiles[18], even though it is not always possible to make this distinction. An example is the ApoE polymorphism, which might predict a patient's response to statins[19] or the risk associated with discontinuation of statins[20], but it also predicts a patient's risk of developing Alzheimer's disease[21]. Such polymorphisms might lead to difficult decisions for health care professionals. Is it the task of health care professionals to tell the patient about this risk? The patient, of course, has the right (not) to know. This information might not only influence the patient, but also members of his family who might carry the same polymorphism. Furthermore, it might not only influence the patient's perception of his health and life, but also his eligibility for healthcare and life insurance. On the other hand, medical information, such as a family history of diseases, also applies to other family members. This information and other risk indicators, such as total cholesterol and blood pressure levels, are already being used to assess a subject's risk and insurance premium. The debate continues in various countries, so far with an uncertain outcome. Pharmacists and physicians should be active participants in this process as they know the practice of pharmacy, patient needs and the economics of the market place[22].

Even though there are high expectations of developments in the implementation of (pharmaco)genetics in health care in the next decade, it is important to realise that, with the exception of relatively rare single gene disorders, genetic tests differ little from most other medical tests, providing evidence of statistical risk only[23]. Inflated perceptions of the value of specific genetic tests could drive a wave of inappropriate medicalisation. The antidote to genetics as a driver of medicalisation lies in a continuing scepsis. Genetic claims, tests, and products should be subject to rigorous evaluation[23].

In our view, pharmacogenetics needs to be implemented in health care practice[22]. To make that possible, health care professionals and patients need to have access to reliable information, from independent sources, about tests and medicines[1]. The computer software in the pharmacies may be able to discover drug–gene interactions for a particular patient, just as drug–drug interactions and contraindications are signalled by computer software now. When physicians and pharmacists have sufficient knowledge about new developments they will be able to contribute to the improvement of pharmacotherapys[24].

In a recent report, the Nuffield Council on Bioethics warns that pharmacogenetic testing is still in an embryonic stage, partly because no accurate or easy-to-use genetic tests are available at present[25].

While the medical possibilities continue to advance, the health-care costs have increased during the past decades and cost containment has been an important goal for policy makers. Using pharmacogenetics to individualize drug therapy may have clinical and economic benefits. However, these benefits must be weighed against the additional cost of genotyping all patients to adjust therapy, sometimes for only a few. Pharmacogenetics will be cost-effective only for certain combinations of disease, drug and gene[26]. Therefore it is important that, besides pharmacogenetic studies, cost-effectiveness studies should be performed. In a recent cost-effectiveness study we showed that, if the interaction between the ACE insertion deletion genotype and the efficacy of statins is confirmed in larger studies, it is cost-effective to screen all men for this genotype before starting statin therapy[27]. If many people have to be tested to prevent only a few adverse events, as is the case in the interaction between factor-V Leiden and oral contraceptives, cost-effectiveness may be enhanced if not all women who start contraceptives are tested, but only those with a high risk of deep venous thrombosis, for example, if

the woman has already had a venous thrombosis or if she has relatives who have had a venous thrombosis at an early age. Such women have a greater chance of being homozygous for the factor-V Leiden mutation. Homozygous carriers may have more than a 100-fold increased risk of venous thromboembolism if they use oral contraceptives[28]. For other interactions it may also be a possibility to only test patients at high risk.

There are many new opportunities in this field for the pharmacist to stress his distinctive features as a health care professional. When practical and ethical issues are resolved, pharmacists should be ready to implement pharmacogenetics in daily practice.

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