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INTRODUCTION

Individuals respond differently to drug therapy, both in terms of beneficial and adverse effects. Important factors that contribute to the variability in outcome of drug therapy include the patient's health profile, prognosis, disease severity, quality of drug prescribing and dispensing, compliance with prescribed pharmacotherapy, and last, but not least, the genetic profile of the patient (1). Pharmacogenetics studies to what extent variability in genetic makeup is responsible for the observed differences in therapeutic efficacy and adverse reactions among patients. The aim of pharmacogenetics is to shape therapy with available medicines in an individualized fashion.

This article provides an overview of current thinking and experience on the application of pharmacogenetic concepts. We will start by discussing the importance of pharmacogenetics in drug therapy. On the basis of several examples, the relevance of currently available knowledge of gene-drug interactions for clinical practice will be discussed in the next section, and we will complete this article with a discussion of challenges for the pharmacist in implementing pharmacogenetics in pharmaceutical care and management.

PHARMACOGENETICS

Problems with drug therapy can be divided into two categories. The first problem is that drugs do not work for all patients. In Table 1 the response rates of patients to several important drug categories are shown. Only 60% of the patients using selective serotonin reuptake inhibitors (SSRIs), antipsychotics, or antiasthma drugs are responders. The other 40% do not respond to the therapy. Drugs that are used in Alzheimer's disease or chemotherapeutics are only effective in 30% and 25% of patients, respectively. This means that most patients using these drugs (with risk of annoying side effects) do not experience beneficial effects. If it were possible to predict in advance whether or not a patient would react to a drug, this would save inconvenience for the patient and also save costs. Especially in chronic therapy, it is very important that the therapy fits the patient because of the heavy burden of lifelong therapy and because of the high costs involved.

TABLE 1. Response Rates of Patients to Important Drug Categories.

Therapeutic category	Efficacy rate (%)
Alzheimer drugs	30
COX-2 inhibitors	80
SSRIs	60
Chemotherapy	25
Asthma	60
Antipsychotics	60

Prescription Desk Reference, 2000.

The other major problem in drug therapy is adverse events. More than 2 million hospitalized patients have severe adverse drug reactions annually in the United States, 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). Some adverse drug reactions caused by genetic variation that were previously considered not preventable may now be preventable (4). Recently, cerivastatin was withdrawn from the market because of an increasing number of reports of side effects. Genetic identification of patients with high risk for adverse events might prevent unnecessary withdrawals. The drug could be targeted to patients who are likely to respond and who are unlikely to experience side effects.

EXAMPLES IN CLINICAL PRACTICE

In this section, we will describe several examples of pharmacogenetic interactions (Table 2). The first example is a pharmacokinetic interaction. Subjects who are homozygous for the cytochrome P450 enzyme 2D6 (CYP2D6) null alleles exhibit a "poor metabolizer" phenotype, which occurs in 6% to 10% of Caucasians. Other genotypes for this enzyme (on chromosome 22) lead to phenotypes that can be classified as extensive or ultra-rapid metabolizers. Cytochrome P450 2D6 is involved in the metabolism of many cardiovascular drugs and antipsychotics. Subjects with the "poor metabolizer" phenotype have a higher risk of developing extrapyramidal side effects when they use

TABLE 2. Examples of Pharmacogenetic Markers.

Involved polymorphisms	Pharmacogenetic effect
Cytochrome P450 (CYP) 2D6	The CYP2D6 defect leads to a "poor metabolizer" phenotype in 6-10% of Caucasians. Metabolizes 25% of all drugs including many cardiovascular drugs and antipsychotics.
Factor V Leiden	Factor V Leiden carriers have a 7 times increased risk of venous thrombosis. In women using oral contraceptives the risk of venous thrombosis is 4 times increased. In women with both risk factors the risk is 36 times increased.
CETP polymorphism	Association with atherosclerosis progression and with response to HMG-CoA reductase inhibitor therapy.
β2-receptor	The polymorphism at codon 16 of the β2-receptor is associated with the deleterious effect of regularly scheduled use of asthma medication.
Apolipoprotein E	The Apo E ε4 polymorphism is associated with risk for Alzheimer's disease and with a poor response to anticholinesterase treatment.

Format according to Kleyn and Vesell, *Science* 1998.

classic antipsychotic drugs (5, 6). In several psychiatric hospitals in the Netherlands, patients are already routinely genotyped for this enzyme.

Another example is the factor V Leiden mutation. The incidence of venous thrombosis among nonusers of oral contraceptives is about 0.8 per 10,000 person years. This risk increases to 5.7 per 10,000 person years for carriers of the factor V mutation. The risk increases to 3 per 10,000 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 10,000 person years, so the gene-exposure interaction is much greater than 1.0 (7). Thus, carriers of the factor V Leiden should use methods of birth control other than oral contraceptives.

Another case is the association between the CETP (cholesteryl ester transfer protein) polymorphism and statin therapy. CETP has a central role in reverse cholesterol transport, the mechanism by which cholesterol is eliminated from the body. Pravastatin therapy slowed the progression of coronary arteriosclerosis in subjects with the wild genotype but not in subjects who were homozygous for the polymorphism. Sixteen percent of the population under study was homozygous for the polymorphism (the B2B2 genotype). This common polymorphism might

be a reason not to treat subjects with statins (8). But CETP is not the only polymorphism involved in the prediction of the effectiveness of statins. In the literature, different polymorphisms have been described (Cholesteryl Ester Transfer Protein polymorphism, Stromelysin-1 polymorphism, -455G/A and Taq I polymorphisms of the beta-fibrinogen gene, ApoE4, Asp_9Asn mutation in the lipoprotein lipase gene, the -514 CT polymorphism in the hepatic lipase gene, and the ACE deletion type gene) that have an influence on the effects of statins in the general population (9). There are probably even more polymorphisms of importance. The cholesterol metabolism is a very complicated process in which many proteins are involved. It will take some time until it is clear which polymorphisms will be needed to predict the effectiveness of statins.

A last example is the use of inhaled selective β2-agonists in asthma. Over the past several years, it has been suggested that regularly scheduled use of inhaled β-agonists is associated with a deleterious effect on asthma control. Israel et al. showed in their trial population that only subjects with a polymorphism at codon 16 of the β2-adrenergic receptor (37% of the population) experienced this deleterious effect, which was not seen when they used the medication as needed (10).

The clinical relevance of polymorphisms that are known to modify drug response is not always clear. Is it always relevant for the individual patient to know the genotype before drug treatment is started? What is the clinical relevance for the entire population? How often does the polymorphism occur in the population, and what is the distribution of it in various subpopulations? What is the burden of avoidable adverse effects when subjects are needlessly treated? Is screening the patient's genotype prior to treatment start cost-effective (11)? A good example of clinically relevant decisions that have to be made is the screening for factor V Leiden of women using oral contraceptives. It would be possible to screen all women using "the pill" or who intend to start using it. This would deny effective contraception to 3-6% of white women while preventing only a small number of cases of venous thromboembolism. The conclusion of Vandenbroucke et al. is that there are certain situations in which it may be wise to determine the genotype, 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 hundredfold increased risk of venous thromboembolism if they use oral contraceptives. This means

that the clinical situation of the patient and her relatives–and not only the genotype–will continue to direct the physician's advice (12).

ROLE OF THE PHARMACIST AND PHARMACEUTICAL MANAGEMENT

In our view, the future of pharmacogenetics needs a strong implementation in the practice of pharmacy. Science will continue to make progress, and it is up to the profession to fit genetic concepts into general practice. In the future, a patient may carry his genetic profile around on a card. The computer software in pharmacies may be able to discover drug-gene interactions for that particular patient, just like drug-drug interactions are signaled by computer software now. When pharmacists have enough knowledge about new developments, they will be able to contribute to reaching the optimal therapy. A key factor in determining the success of genetic pharmacoepidemiology will be access to data on genotype and other relevant molecular markers (1).

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, even though it is not always possible to make this distinction (13). An example is the ApoE4 polymorphism. This polymorphism might predict a patient's response to statins, but it also predicts a patient's risk of developing Alzheimer's disease (14, 15). Polymorphisms like this might lead to difficult decisions for the health care workers. Is it their task to tell the patient about this risk? The patient has, of course, the right (not) to know. And this information might influence not only the patient but also members of his family who might carry the same polymorphism. And it might not only influence the patient's perception of his health and life; it could also affect his chances of obtaining life insurance, for example. This debate is ongoing in various countries with, so far, an uncertain outcome. Experts in pharmaceutical management should be active participants in this process, as they know the practice of pharmacy, patient needs, and the economics of the marketplace.

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 pharmacogenomics to individualize drug therapy will have clinical and economic benefits. However, these benefits must be weighed against the additional cost of

genotyping all patients to adjust therapy for sometimes only a few. Pharmacogenetics will be cost-effective only in certain combinations of disease, drug, and gene. Characteristics favoring cost-effectiveness are a severe outcome (high mortality, significant impact on quality of life, expensive medical care costs), monitoring of drug response currently not practiced or difficult, strong association between gene variant and outcome, a rapid and inexpensive assay for determining gene variant is available, and frequency of gene variant in population is high (16). And what about the economic consequences of tailor-made drugs? Will all personalized drugs become orphan therapies in the future?

There are many new possibilities in this field for the pharmacist to emphasize his distinctive abilities as a health care professional, but there are also many mantraps. In the next few years, it will be very important for pharmacists to update their knowledge. When practical and ethical issues are solved, pharmacists should be ready to implement "pharmacogenetic management."

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