Pharmacogenomics—Potential Applications to Orthopedic Practice

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Pharmacogenomics is developing at a rapid pace. Though ethical and financial considerations still exist, physicians should familiarize themselves with this evolving science.

"If you can dream it, you can do it." - Walt Disney

The idea that a patient may be treated based on their own genetic makeup versus the "one size fits all" approach is no longer beyond the realm of possibility. With the advent of pharmacogenomics, researchers expect that practitioners will be able to select specific medication doses and decrease the number of adverse drug reactions (ADRs) experienced by patients. This new approach to medicine will likely impact all specialties, including orthopedics.

Human Genome Project in 2003 prompted a rapid development in pharmacogenomic and pharmacogenetic research. Pharmacogenomics uses molecular biology techniques such as high-throughput sequencing, DNA and protein microarrays, and bioinformatics to identify genetic determinants of drug response.¹ This is related to pharmacogenetics, a field formally recognized for 50 years, which studies inherited differences in drug metabolism and response. Because the distinction between pharmacogenomics and pharmacogenetics is considered arbitrary, the two terms are often used interchangeably.²

One of the most significant advances in pharmacogenomics has been the discovery of single-nucleotide polymorphisms and haplotypes.³ Single-nucleotide polymorphisms are DNA sequence variations that occur when a single nucleotide (A, T, C, or G) in the genome sequence is altered. A variation must occur in at least 1% of the population to be a single-nucleotide polymorphism.⁴ It is estimated that there are approximately 11 million single-nucleotide polymorphisms in the human population, and an individual's response to a drug and susceptibility to a disease may be influenced by these variations.⁵ The goal of researchers is to identify those single-nucleotide polymorphisms that are relevant markers of drug response and susceptibility to disease.⁶ Sets of single-nucleotide polymorphisms on the same chromosome are inherited in blocks or patterns (haplotypes).⁷ Identifying these haplotypes will likely provide a more useful marker of drug response.³

Currently, most medication doses are chosen on a trial-and-error approach, using different doses until a response is achieved. If a response is not reached using one medication, another may be prescribed on a subsequent visit to the physician. This approach can lead to delays in achieving therapeutic response, possible toxicities, or adverse drug effects. There is also an increase in cost of the overall therapy through increased office/clinic visits as well as the direct cost of the medications. With advances in pharmacogenomics, it is likely that the medication prescribed will be based on an individual's genotype therefore maximizing the benefit of the medication while minimizing adverse effects.⁵

Economically, there may also be an impact of pharmacogenomics by decreasing the overall cost of healthcare. Not only should pharmacogenomics aid in decreasing ADRs or the number of medications tried by an individual patient,⁸ but it also may decrease costs within the pharmaceutical industry by lowering the developmental costs, reducing candidate drug failures, us-

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ing existing products in new ways, or bringing back withdrawn products that could be redirected at certain patient populations. In fact, many pharmaceutical companies are now using pharmacogenetics as a screening method in clinical trials. 3

CLINICAL APPLICATIONS OF PHARMACOGENOMICS

Physicians are currently applying genetic associations to treat their patients in a variety of practice settings. These include predicting doses or toxicity for cancer patients receiving chemotherapy with thiopurines, fluorouracil, or irinotecan. Ongoing studies of lymphoma, leukemia, and breast cancer may also help identify methods to individualize treatment. 5

In cardiology, psychiatry, and pain management, practitioners are already aware of clinical effects that can be attributed to genetic variation. Other areas of investigation will likely impact surgeons, including those within the orthopedic specialty. The effects of genetics on the metabolism, drug interactions, and complications associated with anticoagulation therapy continue to be researched.

WARFARIN

Warfarin has been used >50 years in the treatment and prevention of various thromboembolic disorders. It is well known that both acquired and environmental factors can influence the anticoagulant response to this agent, including age, alcohol intake, weight, diet, and other concomitant medications or disease states. However, despite the importance of these influences, the variation among response to warfarin cannot be explained solely by these factors. Because warfarin has a narrow therapeutic index, its pharmacologic effect is measured closely through use of the international normalized ratio (INR). The rate of hemorrhage is greatest during the initiation of warfarin therapy because it is during this time that the INR is most likely to be out of range. Additionally, existing warfarin dosing algorithms rely on the trial-and-error approach rather than being designed to fit an individual's genetic makeup. 7

Warfarin interferes with the action of vitamin K, which is necessary for the gamma-carboxylation of several glutamic acid residues in the precursor proteins of coagulation factors II, VII, IX, and X. The result is synthesis of dysfunctional forms of these coagulation factors. 8 Oral administration of warfarin results in complete absorption with nearly 99% of the drug bound to albumin within the plasma. The more active form of warfarin, the S-enantiomer, is metabolized via the cytochrome P-450 (CYP-450) enzyme system, the most important being the CYP2C9 complex. 9 Genetic variability in this complex is a major factor in the efficacy and toxicity of this drug. A review by Daly and King 9 states that in at least eight different clinical studies, the presence of CYP2C9 or CYP2C9 variant alleles was associated with the need for a decreased warfarin dose to maintain optimum anticoagulation. For example, the dose of warfarin needed to attain target anticoagulation was 1.5 mg a day for the homozygous CYP2C9 genotype versus 4 to 6 mg for the wild-type genotype. 9 Individuals with the CYP2C9 genotype typically take longer to stabilize on a maintenance dose of warfarin and are at a higher risk of bleeding episodes. 10 Although some research has been conducted with specific ethnic populations, more research is needed to determine how ethnicity is related to the CYP2C9 activity. 11

Drugs that inhibit CYP2C9 such as sulfinpyrazone, amidarone, miconazole, and fluconazole increase the risk of bleeding when administered with warfarin. Therefore, a dose reduction of the warfarin should be considered. Conversely, other agents such as rifampin, barbiturates, carbamazepine, and St. John's Wort increase warfarin's metabolism. For the patients on these enzyme inducers, increasing the dose of warfarin by a factor of two to four may be required to maintain INRs within the desired range. However, with the discontinuation of these agents, the level of CYP2C9 activity gradually returns over a period of weeks. It would therefore be advisable to monitor the INR more frequently as drugs with known interactions with warfarin are prescribed. 12

WARFARIN RESISTANCE

The allelic variations of CYP2C9 do not fully explain the variation in warfarin response among individuals. 13 Another less common phenomenon that occurs in patients receiving warfarin anticoagulation therapy is the need for higher doses to maintain adequate anticoagulation, also known as warfarin resistance. The effect of warfarin on the hepatic synthesis of vitamin K-dependent coagulation factors is reversed by vitamin K. 10 The recent discovery of a warfarin target gene, vitamin K epoxide reductase complex (VKORC1) gene, may help explain how warfarin resistance occurs among individuals. Rieder et al 14 concluded that VKORC1 haplotypes can be used to stratify patients into low-, intermediate-, and high-dose warfarin groups, which may explain the variability among patients of different ancestries in regard to therapeutic warfarin doses.

The investigators found that African Americans had a higher proportion of a particular group of haplotypes while Asian Americans had a higher proportion of yet another haplotype. These differences explained approximately 25% of the variance in dose. 14 If screening for VKORC1 will identify patients' warfarin doses remains to be seen. 13 Since the gene was recently identified in 2004, it is likely that more research will be published with the goal of more accurately predicting warfarin dosing for an individual.
HEPARIN-INDUCED THROMBOCYTOPENIA

Heparin-induced thrombocytopenia is an uncommon but potentially devastating adverse reaction to heparins, both low-molecular-weight heparin and unfractionated heparin. A meta-analysis conducted by Martel et al. recently reviewed the incidence of heparin-induced thrombocytopenia in patients given unfractionated heparin or low molecular weight heparin for thromboprophylaxis. Heparin-induced thrombocytopenia was defined as a drop in platelets >50% or to <100 X 10^9/L and a positive heparin-induced thrombocytopenia assay. The majority of the studies were for postoperative prophylaxis following orthopedic surgeries. They determined the absolute risk of heparin-induced thrombocytopenia with low-molecular weight heparin to be 0.2% and with unfractionated heparin to be 2.6%. There has been conflicting data regarding a gene-heparin-induced thrombocytopenia association with some studies reporting an association with a homozygous 131Arg/Arg genotype whereas investigators have not reported a similar conclusion. The discrepancy in these results may involve the differences in the types of conditions studied (thromboembolic complications versus isolated thrombocytopenia) or in the types of assays used to detect heparin-dependent antibodies. If an association between heparin-induced thrombocytopenia and a polymorphism is confirmed, then genotyping may be used to identify individuals at risk for drug-induced complications so that alternate therapy may be selected.

FUTURE CONCERNS

Understandably, with new technology there are issues related to the privacy of individuals, especially as it relates to personal health. These may include concerns about research, confidentiality, informed consent, the possibility of discrimination, or access to healthcare. If genetic screening becomes more prevalent in clinical trials, the public, as well as health care professionals will need to be educated about the research process, especially regarding informed consent, binding, and reporting of results. The ethical question then may become whether or not there is an obligation to share the results with an individual in that study, especially as it relates to an increased likelihood of developing a particular disease or abnormal response to treatment. How to translate these concerns into practice will be examined by a pilot study, still in the planning stage, conducted by the National Human Genome Research Institute.

REFERENCES


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