Genetics and Drug Response

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Key Points

- Individual response to many drugs is highly variable.
- Genetic differences in drug-metabolizing enzymes and other genes associated with drug effects account for a significant proportion of the variation in drug response.
- In the future, genetic tests to predict drug response — referred to as "pharmacogenetic" (or "pharmacogenomic") tests — are likely to become an important aid in prescribing some drugs, particularly those with narrow therapeutic indices.
- Although some pharmacogenetic tests are already being offered commercially, there are currently no established uses of these tests in primary care practice. This may change in the near future as a result of active research in pharmacogenetics and anticipated new FDA guidance related to pharmacogenetic testing.

Learning Objectives

Participants will be able to:

- Understand the rationale for pharmacogenetic testing;
- Understand the issues to be considered in the future development of practice guidelines for pharmacogenetic tests.

Family History Issues

Although gene variants associated with drug response may be shared by different family members, family history is not been evaluated as a risk factor for poor drug response or adverse events. Many different genes are likely to play a role in a given individual's response to a particular drug.

Red Flags 

Before the use of any drug, patients should be queried about adverse drug

responses and drug allergies. In the future,f genetics may play an important role in identifying patients with a high risk of adverse drug responses.

Case 41. A Patient on Warfarin Asks about Genetic Testing

Mr. S, who is 55, has been on warfarin for about two years, due to his intermittent atrial fibrillation. He is otherwise in good health. During the initial treatment period, he required several adjustments to his Coumadin® dose to achieve an international normalized ratio (INR) in the therapeutic range, but subsequently his dose has stabilized. Then, a few weeks ago, he developed severe bruising, and his INR was found to be above therapeutic range. In retrospect this complication occurred because another physician treated him with an antibiotic for prostatitis, without adjusting his warfarin dose. His warfarin dose was temporarily reduced; he has completed his antibiotic treatment and his INR is now back in the target range on his usual dose.

Mr. S has returned for follow-up. He mentions a Web site that offers genetic testing of a drug-metabolizing enzyme, CYP2C9, to determine genetic response to warfarin, and wonders if he should have this test.

Clinical Care Issues

All drug therapy carries the potential for adverse effects. Drugs with narrow therapeutic indices and serious associated risks, such as warfarin, require careful monitoring. The standard of care for patients on warfarin includes periodic assessment of the patient's INR and clinical status, with the surveillance interval determined by the patient's clinical stability. In addition, warfarin therapy should be taken into account when any other drug therapy is considered because of synergistic effects or drug-drug interactions that could result in excess anticoagulation.

Risk Assessment

All patients on warfarin should be considered at risk for bleeding complications. Risk management occurs through careful monitoring of the INR level during initiation and maintenance of therapy. Other therapies can

influence INR level, through an effect either on drug metabolism or gastrointestinal vitamin K production. Several antibiotics may reduce vitamin K level by their effect on gastrointestinal flora that are an important source of vitamin K. Therefore, warfarin dose may need to be decreased during antibiotic therapy.

Genetic Counseling and Testing

Variants in the *CYP2C9* gene have been shown to be associated with an increased risk of bleeding complications from warfarin treatment. Tests for these variants might help to identify patients who would benefit from lower loading doses or more careful monitoring of their warfarin therapy. However, *CYP2C9* variants do not account for all the variation in individual response to warfarin, and there are currently no prospective data to assess the outcome of genetic testing for *CYP2C9* variants in patients receiving warfarin therapy. Thus, this type of genetic testing, while theoretically of potential clinical benefit, has not yet been fully assessed for use in clinical practice.

Interventions

No interventions are currently recommended for stable warfarin-treated patients based on genetic risk.

However, active research is underway in pharmacogenetics. Primary care providers should be prepared for new information that may provide justification for pharmacogenetic testing. In the case of warfarin therapy, *CYP2C9* testing would be justified if well-designed clinical trials showed that dosing or surveillance based on *CYP2C9* genotype resulted in fewer adverse bleeding events and equivalent control of thromboembolic events, compared to usual practice.

Ethical/Legal/Social/Cultural Issues

Pharmacogenetic testing is widely discussed as an important benefit of genomic research. The association between *CYP2C9* gene variants and warfarin response represents an example of the potential benefits that might emerge from genetic research on drug response.

However, premature use of this testing option could have several negative effects:

- False reassurance, and possibly insufficient monitoring, for patients on

warfarin who do not have the gene variants associated with higher risk
- Inadequate anticoagulation or discontinuation of therapy in those who carry the risk-associated variants
- Worry or stigma as a result of a positive genetic test, particularly if significance of results is overestimated
- Failure to evaluate the testing strategy via controlled clinical trials, with the result that the outcomes of testing are never fully assessed

In addition, the prevalence of *CYP2C9* variants associated with poor metabolism of warfarin varies by racial/ethnic background. Thus, if research documents clinical utility for this testing approach, policy makers will need to consider whether race/ethnicity should be a factor in determining who should be tested.

Primary care providers need to be aware that pharmacogenetic testing is currently in development. Professional organizations can play an important role in practice guideline development by insuring that guidelines are based on adequate outcome data and appropriate consideration of potential benefits and harms.

Related Information

Box 1: Current example of pharmacogenetic testing

A pharmacogenetic test related to the care of children with acute lymphoblastic leukemia (ALL) is now frequently used, and may represent the best current example of a pharmacogenetic test. The test identifies patients who carry variants in the gene coding for the enzyme thiopurine methyl transferase (TPMT). These variants are associated with low enzyme activity and greatly increase the risk of life-threatening reactions to mercaptopurine, a drug used in the treatment of ALL. Approximately one in three hundred children is homozygous for a TPMT variant associated with adverse outcomes, and 5% to 10% of the population are heterozygous; genetic testing of children being treated for acute leukemia makes it possible to reduce exposure to mercaptopurines in the relatively small number of children at risk.

Box 2. The concept of pharmacogenetic profiling

The cytochrome P450 genes (also referred to by the designation *CYP*) are a family of genes that code for drug-metabolizing enzymes. Common variants in these genes are associated with differing levels of enzyme function, and, for many drugs, play a major role in determining the fraction of an oral dose that reaches the systemic circulation. Some of the more common medications metabolized by P450 enzymes are listed below, though it is important to keep in mind that P450 metabolism may provide only part of the complete drug metabolism, and some drugs do not undergo significant metabolism. For a more complete list of drugs metabolized by cytochrome P450 genes, see Drug Interaction Table (Cytochrome P450 System).

- Cytochrome P450 2D6 (also designated CYP2D6) affects metabolism of fluoxetine, sertraline, paroxetine, venlafaxine, hydrocodone, amitriptyline, haloperidol, metoprolol, cimetidine, tamoxifen, fexofenadine, loratidine.
- Cytochrome P450 2C9 (also designated CYP2C9) affects metabolism of warfarin, sulfa drugs, ibuprofen, phenytoin, naproxen, sildenafil.
- Cytochrome P450 2C19 (also designated CYP2C19) affects metabolism of valium, phenytoin, conjugated estrogens, lansoprazole.

Rapid metabolizers may be resistant to drugs because sub-therapeutic levels of the drug make it into circulation (i.e., the rapid metabolism causes enhanced clearance). Poor metabolizers, on the other hand, may be sensitive to the same drugs and may be more prone to adverse events due to toxic drug concentrations (i.e., poor metabolism retards clearance). It is possible to be a rapid metabolizer for drugs in the CYP2D6 pathway, an efficient metabolizer of drugs in the CYP2C9 pathway, and a poor metabolizer of drugs in the CYP2C19 pathway, or in any other combination. These observations have led to the concept of pharmacogenetic profiling as a potential means to predict individual responses to a wide range of drugs. However, few associations between P450 (or *CYP*) genotype and clinical outcomes have been clearly established, and the appropriate clinical use of such information remains to be determined (see case example).

References

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