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Preparing for the Genomic Age: Thiopurine S-Methytransferase Polymorphism

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Abstract
Interpatient variability among medication doses has been a longstanding obstacle for many prescribers. Some medications result in increased morbidity and mortality in a small percentage of the population. For many years, the cause of such toxicities was unknown. This mystery has been resolved by the discovery that the absence or abnormality of specific genes that code for receptors, drug targeted proteins, drug transport mechanisms and drug metabolizing enzymes could alter how an affected individual will respond to a given drug. One such incidence is the genetic polymorphism in thiopurine s-methyltransferase (TPMT). In comprehending the mechanism of this polymorphism, it is important to understand the metabolic pathway of thiopurine drugs. Through study of this pathway, researchers began to look into whether other polymorphisms aside from TPMT could be a source of the dose-related toxicity with the thiopurines. The prospect that this polymorphism may contribute to an increase in number or exacerbation of side effects beyond the commonly presented bone marrow toxicity also has been visited. Becoming more aware of this genetic issue has presented the need to evaluate the cost effectiveness of genetic testing to counteract the expected cost of treating extreme myelosuppression. Having knowledge of new pharmacogenomic technology and the tests available can benefit pharmacists in any setting. Pharmacists will be more prepared to address patient concerns such as necessity and cost effectiveness.

Introduction
Recently, opinion articles were published in the New England Journal of Medicine that discussed the controversies surrounding genetic testing and, in particular, the marketing of this testing directly to consumers. As pharmacists, we must be aware of these advances as we enter into the “genomic” age and how they may impact our patients. In this article, we present a case study of thiopurine s-methytransferase polymorphism.

Ten to 28 percent of patients receiving azathioprine or mercaptopurine therapy experience toxicity that requires stopping treatment or, in severe cases, results in death. Recognizing that this well-known occurrence is related to a genetic polymorphism in thiopurine s-methyltransferase (TPMT) has provided insights into the mechanism of intolerance and offered strategies to avoid these toxicities.

Numerous medications exhibit wide interpatient variability in efficacy and toxicity. Although nongenetic factors influence the effects of medications, the variability in response is many times due to single nucleotide polymorphisms (SNPs) in genes encoding drug-metabolizing enzymes, drug transporters and/or drug targets. Initial reports from the human genome project described over 1.4 million SNPs in the genome, but this number continues to grow with extended research. There are more than 30 families of drug-metabolizing enzymes in humans, all with genetic variants causing the translation of such proteins to result in functional differences. Patients who inherit a drug-metabolizing enzyme deficiency must be treated with markedly different doses of the affected medications. Therefore, identifying genetic determinants of drug response can help optimize the selection of drug therapy.

TPMT polymorphism
One of the most understood examples of a genetic polymorphism is that of TPMT, which catalyzes the s-methylation of azathioprine, mercaptopurine and thioguanine. These medications, together called the thiopurine drugs, are widely used in the treatment of leukemia, inflammatory bowel diseases and severe rheumatic diseases and for immunosuppression following solid organ transplantation. Azathioprine, mercaptopurine and thioguanine are all inactive prodrugs requiring activation to thiopurine nucleotides. The active nucleotides compete with endogenous nucleotides in many biochemical pathways, such as the synthesis of DNA accounting for the immunosuppressive effects of these drugs. These thiopurine drugs can undergo s-methylation by TPMT or oxidation to thiouic acid by xanthine oxidase to be inactivated (figure 1). Due to this alternative degradation pathway, the importance of the TPMT polymorphism is diminished in most tissues. However, hematopoietic tissues do not have measurable xanthine oxidase activity, leaving s-methylation as the major competing metabolic pathway. Patients who inherit TPMT deficiency accumulate excessive concentrations of the active thioguanine nucleotides in blood cells. This causes a heightened immunosuppressive reaction, leaving the patient at high risk for developing bone marrow toxicity, resulting in pancytopenia, a reduction in red blood cells, white blood cells and platelets. TPMT is not known to be involved in any pathway for endogenous substrates.

Figure 1: Azathioprine Metabolism

Azathioprine

6-mercaptopurine

TMPT

xanthine oxidase

6-methylmercaptopurine (inactive)

6-thiouic acid (inactive)
Studies have been conducted to assess whether other genetic variations, aside from a TPMT polymorphism, affect azathioprine toxicity. A study from the Department of Pharmacology at Pomeranian Medical University in Poland investigated the role of another enzyme, inosine triphosphate pyrophosphohydrolase (ITPA), which takes part further down the metabolic pathway of thiopurines. The goal of the study was to determine if azathioprine drug intolerance was related to ITPA allele variants. ITPA catalyzes the dephosphorylation of inosine triphosphate (ITP) to inosine monophosphate (IMP). A lack of ITPA leads to an excess of ITP, which has not been proven to be pathogenic. However, some researchers have noted that an accumulation of ITP during azathioprine therapy can produce metabolites (such as thio-ITP), which may interfere with normal metabolic activity. The cohort study was conducted with a large group of renal transplant patients. Patients were evaluated for TPMT genetic polymorphisms and monitored for adverse effects of low white blood cell (WBC) count and hepatotoxicity. It was observed that ITPA had no effect on liver toxicity, and there was no statistical evidence that ITPA altered WBC count. Though previously determined in numerous other trials, the genetic effect of TPMT variations was confirmed yet again. Authors of the study concluded that genetic testing for ITPA during thiopurine immunosuppressive therapy is not beneficial at this time because there is no statistical significance that it plays a role in adverse effects.

It also has been determined that 10-30 percent of patients cannot tolerate thiopurine therapy because of additional adverse events such as hepatotoxicity, pancreatitis, influenza-like symptoms and nausea. A cohort study conducted in a small group of Greek pediatric patients diagnosed with inflammatory bowel disease (IBD) observed the relationship between these adverse events and TPMT deficiency. A group of just under 100 children (mean age 11.5 years) undergoing treatment of IBD with thiopurines was monitored for adverse events based on their genetic makeup in regards to their ability to metabolize TPMT. This study was conducted with the assumption that patients with a genetic variant that translates to poor TPMT activity experienced higher rates of the previously mentioned adverse events. Authors of the study concluded that, while dosages needed altering based on phenotype, the noted adverse events did not correlate with genetic variation.

The TPMT genetic polymorphism serves as a good example of the importance of pharmacogenetics because it has been well characterized at the molecular, biochemical and clinical levels. The importance of this polymorphism is appreciated because its effect is highly penetrant when TMPT-deficient patients are treated with standard doses. This means that essentially 100 percent of TMPT-deficient patients will develop hematopoietic toxicity. Approximately 11 variant alleles have been associated with low TPMT enzymatic activity in humans. These alleles contain SNPs leading to amino acid substitutions, formation of a premature stop codon or destruction of a splice site. TPMT*3A is the most prevalent mutant in whites while TPMT*C is the predominant mutant allele in Asian, African and African-American populations.

Conclusion

Polymerase chain reaction tests provide a means of prospectively identifying these patients prior to drug therapy, thereby minimizing toxicities. Although all studies have been done based on rough estimates, research points to the cost effectiveness of such testing by comparing it to the expected cost of treating extreme myelosuppression. It is estimated that, by predetermining a case of TPMT deficiency, nearly $3,000 could be saved in health care costs per patient. This data clearly shows that, aside from the lives that can be saved, genetic testing has an extremely positive impact from an economic standpoint. Even so, health care providers must remember that cautious monitoring of blood counts is required in all patients, since myelosuppression with thiopurine drugs can still occur in patients with normal TPMT activity.

References