Recent advances in molecular biology have provided physicians with genetic testing strategies that can be used to predict adverse drug reactions (ADRs). Many ADRs can be linked to single-nucleotide polymorphisms in genes that control aspects of drug disposition. We report a case in which a standard dose of methotrexate resulted in life-threatening mucositis, neutropenia, and thrombocytopenia in a 61-year-old woman. The patient was found to have a genetic anomaly in an enzyme that plays a key role in folate metabolism. Methotrexate is known to deplete folate levels. As data accumulate and genetic testing strategies improve, it should be possible to predict ADRs in individual patients, thereby resulting in better patient care and a reduction in medical expenditures.

Mapping a relationship between medications and patients’ adverse drug reactions (ADRs) has relied on trial and error, with little insight into the etiologic mechanisms behind poor outcomes with specific pharmacologic agents. Historically, a pharmacokinetic profile for a given medication is determined first in animal studies and subsequently in healthy volunteers.1 These profiles are intended to determine doses that produce maximum efficacy and minimum toxicity. Until recently, there has been scant insight into why ADRs occur in certain individuals.2 In some instances, ADRs can be explained by concurrent medication use, alcohol consumption, tobacco use, hormone levels, reduced hepatic and renal function, age, or body mass index. It has become apparent that many random episodes of severe toxicity or inadequate therapeutic response may be explained by genetic differences in drug metabolism.3 These genetic differences are often the consequence of single nucleotide polymorphisms.4

Single nucleotide polymorphisms are commonly occurring single variations in the order of the nucleotides that constitute DNA.5 Such variations can dramatically alter the synthesis of proteins important to the metabolism of or response to many pharmacologic agents.6 Thus, the emerging field of pharmacogenetics, which explores the contribution of genetic differences to drug response, has provided insight into the origin of many ADRs.7 These considerations are particularly important when drugs with narrow therapeutic indexes or those typically administered at or near their maximum tolerated doses are prescribed.

Methotrexate (MTX) is a drug with a narrow therapeutic index and widespread clinical indications. Therefore, it is especially important for physicians to be cognizant of a possible genetic predisposition to an ADR in response to MTX. The clinical indications of MTX include asthma, cancer, dermatomyositis, ectopic pregnancy, inflammatory bowel disease, lupus erythematosus and its cutaneous manifestations, multiple sclerosis, primary sclerosing cholangitis, psoriasis, pyoderma gangrenosa, rheumatoid arthritis, sarcoidosis, and spondylarthropathy.8 Methotrexate is also a folate antagonist that has been shown to inhibit a number of enzymes in the folate pathway, thereby depleting the available folate pool.9 We report a case in which a single dose of MTX (12.5 mg) resulted in severe toxicity in a patient.

**Report of Case**

A 61-year-old woman was admitted to the hospital because of an increasingly severe headache and focal motor seizures. Enhanced magnetic resonance imaging and subsequent biopsy revealed a bifrontal glioblastoma multiforme with leptomeningeal extension. The patient’s medical history was not clinically significant. There were no reported drug allergies, metabolic or organ abnormalities, or use of drugs known to alter metabolism of MTX. The patient was given a single 12.5-mg dose of MTX as part of her treatment regimen. Within 24 hours, severe oral mucositis, neutropenia, and thrombocytopenia developed. Rescue leucovorin was administered. Over the course of 20 days, the mucositis and myelosuppression gradually resolved. Further MTX was withheld at that point, and an alternative treatment regimen was administered. Subsequent microarray analysis revealed that the patient...
had a homozygous genotype for the C677T mutation of the methylenetetrahydrofolate reductase (MTHFR) gene.

Comment
The enzyme MTHFR metabolizes folate, which serves a major role in nucleotide synthesis. A common mutation in the MTHFR gene is an alanine for valine substitution in the DNA coding sequence at codon 222, called C677T polymorphism. The homozygous mutant genotype occurs in 10% to 15% of the population and confers about 30% of normal enzyme activity. The heterozygous genotype is seen in 30% to 40% of the population and confers 60% of normal enzyme activity. The relevance of this polymorphism has been demonstrated in clinical trials showing a strong association between the C677T polymorphism and severe myelotoxicity. Polymorphisms, which can dictate drug metabolism and/or action, have been shown to influence individual responses to various medications.

In the United States, ADRs result in approximately $4 billion in medical expenses per year. With the availability of pretreatment genetic testing, many life-threatening ADRs can now be predicted with great accuracy. Such testing should result in better outcomes for patients who are at risk for life-threatening ADRs, while allowing gains in cost-benefit for both patients and society.

Routine pretreatment testing could have averted the ADR in our patient. Either a reduced dose of MTX or an alternative agent would have been indicated. In a more general context, testing for common gene polymorphisms known to significantly alter drug metabolism should become routine before medications with narrow therapeutic indices are administered. The current case illustrates the importance and value of genetic testing before initiating drug therapy.

References