MedicalXpress

Gene mutation increases drug toxicity, rejection risk in pediatric kidney transplants

February 18 2009

Screening for mutations in a gene that helps the body metabolize a kidney transplant anti-rejection drug may predict which children are at higher risk for side effects, including compromised white blood cell count or organ rejection, according to new research.

Published online Feb. 18 by the *Nature* journal *Clinical Pharmacology and Therapeutics*, the study suggests this genetic approach could also help physicians tailor personalized anti-rejection drug doses to prevent adverse reactions, said senior investigators Alexander A. Vinks, Pharm.D., Ph.D., and Jens Goebel M.D., of Cincinnati Children's Hospital Medical Center.

"There are better ways than just giving standard doses of these drugs, and in due course these types of technologies will be available worldwide to help patients," said Dr. Vinks, director of the Division of Clinical Pharmacology and the Pediatric Pharmacology Research Unit at Cincinnati Children's. "This pilot study shows personalized and prospective MMF dosing and monitoring may be feasible to reduce the high incidence of drug toxicity in children without compromising the drug's protective effects against kidney graft rejection."

MMF, or Mycophenolate Mofetil, is an immunosuppressive agent commonly used to prevent rejection in organ transplants, particularly in kidney transplants. After taken orally, the drug is quickly processed by the body into active form. During this time, patients with a specific point mutation in the gene that helps break down the drug, UGT, metabolize

the drug slower. This point mutation, called UGT1A9-331, causes overexposure and adverse side effects in the affected children, the study concluded. UGT encodes the drug's main metabolizing enzyme in the body, uridine diphosphate-glucuronosyl transferase.

Adverse side effects most commonly linked to MMF have included gastrointestinal complications (such as diarrhea) or leukopenia - a drop in white blood cell count that can put patients at higher risk for infections. In some instances, patients have to be taken off the drug or have their dosage reduced to the point where they risk rejection of the new organ.

The current study analyzed 38 children who had received kidney transplants. Sixteen of the children experienced adverse side effects from MMF therapy. In the adverse reaction group, nine children with the specific UGT point mutation developed leukopenia. The researchers found no strong association between UGT gene variants and diarrhea - the most common side effect linked to MMF - suggesting gastrointestinal reactions to the drug may be caused by other factors.

Some previous studies have linked UGT gene mutations and MMF-related side effects in kidney transplant recipients, while others have suggested a greater risk for adverse events in children. A review of earlier research combined with their current data led researchers in this study to conclude that pediatric kidney transplant recipients on MMF therapy have a significantly higher likelihood of drug-related complications than adult patients. One previous study compared 22 pediatric and 37 adult transplant recipients, all who started with the standard recommended doses of MMF. Among the children, 54.5 percent experienced adverse side effects compared to 21.6 percent of the adults.

Besides the UGT1A9-331 point mutation, other studies have also linked

a second variation, called UGT2B7-900, to possible MMF overexposure and development of leukopenia, said Tsuyoshi Fukuda, Ph.D., co-author on the current study and a colleague in Dr. Vinks' division at Cincinnati Children's. The research team recently completed pharmacokinetic and biomarker studies - which analyze how the body metabolizes a drug - to solidify the connection between different variants of UGT and MMF overexposure in pediatric kidney transplant patients.

Researchers want to use data from these pharmacokinetic studies as a basis for showing whether increased MMF exposure in adults can also be linked to specific variations in the UGT gene, according to Dr. Fukuda.

The pilot study is part of the growing field of genetic-based pharmacology, or pharmacogenetics. Combining biology and information technology, researchers are developing computer-based algorithms that allow taking a few drops of blood and analyzing how quickly a person's body will break down and absorb a drug based on their genetic makeup. The goal is to reduce drug-related side affects by optimizing drug doses for individual patients.

Source: Cincinnati Children's Hospital Medical Center