YaleNEWS

Yale Researchers Discover Why a Common Antibiotic Causes Deadly Heart Condition in Some

September 13, 2000

A gene present in about 1.6 percent of the general population places these persons at risk for a life-threatening heart rhythm disorder when they take the common antibiotic trimethoprim-sulfamethoxazole or Bactrim(tm), Yale researchers have found.

The heart rhythm disorder is called long QT syndrome (LQTS). Previous studies had shown that rare inherited mutations could produce the disorder. Drug-induced LQTS is a common and equally dangerous condition whose widespread basis has been unclear. This new Yale study shows that a common gene variant that is not harmful by itself can create a risk for a lethal response to the medication.

"Our findings argue for development of genetic approaches to drug therapy to identify patients likely to benefit from treatment and those at risk for side-effects," said Steve A. N. Goldstein, M.D.,Ph.D., associate professor of pediatrics and cellular and molecular physiology, and chief of the Section of Developmental Biology and Biophysics at Yale School of Medicine.

Goldstein, principal investigator on the study, which appears in the current Proceedings of The National Academy of Sciences (PNAS), said the findings also show that like other common diseases such as breast cancer or hypertension, drug-induced arrhythmia is a disorder that develops when multiple factors are present.

Normal heartbeats are due to the orchestrated opening and closing of proteins called ion channels. Ion channels act as pathways for ions across cell membranes. Potassium channels pass potassium ions and in the heart act to end each beat.

The study shows that a variant of a potassium channel gene present in some people places them at risk for LQTS and lethal arrhythmia when they take the antibiotic trimethoprim-sulfamethoxazole. The variant is a change of a single DNA base in the KCNE2 gene. This type of change is called a single nucleotide polymorphism (SNP) and is the most common genetic variation seen between individuals. This SNP produces channels whose functions are blocked by normal blood levels of sulfamethoxazole. The study demonstrates that drug sensitivity is influenced by SNPs.

"While an abnormal electrocardiogram is seen with inherited LQTS and indicates patients who should not take certain drugs -- such as those that affect ion channels in the heart -- individuals with this KCNE2 SNP have a normal electrocardiogram until they take sulfamethoxazole," said Goldstein. "Our study supports the importance of international efforts to complete the sequence map of the human genome including a catalog of its most common variants, the SNPs. In the future, this should help doctors choose the safest medication for each patient based on their genetic make-up."

"The work does not indicate that sulfamethoxazole is a major public health risk," Goldstein adds. "Trimethoprim-sulfamethoxazole is an extremely beneficial agent that has not been frequently associated with arrhythmia despite its widespread use and the prevalence of this SNP."

Goldstein's research team at Yale included Federico Sesti, and Geoffrey W. Abbott. The team also included Katherine T. Murray, Dan M. Roden and Alfred L. George, Jr. of Vanderbilt University; Sanjeev Saksena of The Robert Wood Johnson Medical School; and Silvia G. Priori and Peter J. Schwartz of the University of

Pavia in Italy.