THE COMBINATION OF TWO SNPS IN THE ABCC2 GENE, CODING FOR MULTIDRUG-RESISTANCE-RELATED PROTEIN 2 (MRP2), INFLUENCES INDIVIDUAL PERCEPTION OF HEAT PAIN INDEPENDENTLY OF CLINICAL RESPONSE TO MORPHINE IN HUMAN VOLUNTEERS.

Konrad Meissner MD, PhD; Christine Goepfert MD, PhD; Henriette E.U. Meyer zu Schwabedissen; Jane Blood; Karen A. Frey; Hee Seung Ki; Evan D. Kharasch

Universitätsmedizin, Greifswald, Germany

Summary: Several findings indicate a role for ABC-type (ATP-binding cassette) drug efflux transport proteins in influencing the variability of clinical opioid effects. This phenomenon is attributed to variations in expression and activity secondary to genetic and environmental factors, leading to variable effect site concentrations. Multidrug-resistance-related protein 2 (MRP2, ABCC2), which is expressed in the liver and brain, is known to transport drugs and metabolites (i.e. morphine-6-glucuronide), and has been shown to influence opioid disposition in rodents. The two SNPs 3563T>A (rs17222723) and 4544G>A (rs8187710) are known to influence MRP2 activity in humans.

The present study investigated the influence of two MRP2 variants on morphine disposition and clinical effects (pupil diameter and heat pain response) in 51 healthy human volunteers, who received 0.2 mg/kg morphine over 2 hours. ABCC2 genotype was studied using Sequenome ™ technology and TaqMan™ analysis.

The 3563T>A variant was found in 3 heterozygous subjects, who were also heterozygotes for the 4544G>A variant. Another three subjects were carriers of the 4544A allele only. No homozygous carriers were found for either SNP. At baseline, prior to opioid administration, double mutant carriers were found to tolerate a significantly higher temperature (49,7 ± 1,1°C) compared to both wildtype (47,4 ± 1,6°C) and 4544A-only carriers (47,5 ± 1,6°C). These findings were confirmed in a second reading on another day (49,9 ± 1,7°C vs. 47,1 ± 1,9°C vs. 48,4 ± 1,4°C). Double mutant carriers did not exhibit any increase in maximally tolerated temperature after 2 hours of morphine infusion (0.04°C), whereas wildtype (0.47°C) and 4544A-only (0.57°C) carriers did. Morphine and morphine-6-glucuronide plasma concentrations were similar in all genotype groups.

We conclude that the simultaneous occurrence of 3563A and 4544GA in the ABCC2 gene may contribute to an elevated heat pain tolerance, which cannot be influenced by morphine. This phenomenon cannot be readily explained by drug serum levels and therefore warrants further investigation.

The study was funded by grants from the Barnes-Jewish Hospital Foundation to KM and NIH R01-DA14211, and K24-DA00417 to EDK and RR024992 to Washington University.