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GUEST EDITORIAL

Genetic polymorphisms in the UDP-glucuronosyltransferase UGT1A7 gene in patients with acute liver failure after kava-kava consumption

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Letter to the Editor,

Stickel and Shouval have provided an excellent review in this journal (Stickel and Shouval 2015) addressing the mechanisms of liver toxicity induced by herbal dietary supplements. Among these agents, they included the herbal antidepressant kava-kava, which was withdrawn from the USA and European markets by regulatory authorities because of a significant number of reported cases with severe kava-kava-induced liver injury (Kraft et al. 2001). Since kava-lactones are eliminated by hydroxylation and demethylation steps, several studies have investigated the CYP2D6 gene and identified poor metabolizers to be more prone to kava-kava hepatotoxicity. Additionally there is evidence that the catalytic activity of CYP2C19 can be inhibited by herbal products, including kava-kava, providing further evidence for an association between this cytochrome and hepatotoxicity.

We have identified four patients with kava-kava-induced liver toxicity, all of which developed liver failure and their genetic profile may hint to an alternative pathway of kava-kava associated liver injury. More than 50 % of kavalactones undergo urinary excretion, and therefore glucuronidation may represent an important elimination pathway for kava-kava metabolites. Uridine diphosphate (UDP)-glucuronosyltransferases (UGTs) are important mediators for the inactivation and excretion of various endogenous and exogenous compounds because of their involvement in glucuronide conjugate formation. Polymorphisms of the UGT1A7 gene were found to be associated with various liver diseases including an association of hepatocellular carcinoma with the low detoxification activity of the UGT1A7*3 isoform and UGT1A7 variations with liver cirrhosis (Vogel et al. 2001).

In our patients with fulminant liver failure, the ingestion of kava-kava for mild depression was the only identifiable risk factor. All had developed liver dysfunction with jaundice, encephalopathy, and marked elevation of liver enzymes, and three of them ultimately needed liver transplantation. Only one patient had previously taken etilefrine and piretanide, whereas all other patients had no co-medication. In all four, we sequenced the UGT1A7 gene using standard protocols (Keim et al. 2001). In brief, DNA was extracted from whole blood using QIAamp® DNA Mini Kit (QIAGEN, Hilden, Germany). Exon 1 of the UDP-glucuronosyltransferase UGT1A7 was amplified using the sense primer 5′-CTT CCA CTT ACT ATA TTA TAG GAG C-3′ and 5′-CCA TAG GCA CTG GCT TTC CCT GAT G-3′ for the antisense strand (GeneBank Accession Number: U89507). After purification, DNA fragments were sequenced using an ABI Prism® 3700 DNA Analyzer (Applied Biosystems, Carlsbad, CA, USA). Chromatograms were analyzed using Chromas 1.61 software. Distribution of allele frequency in controls and data about enzymatic activities of corresponding UGT1A7 isoforms were taken from recent publications (Guillemette et al. 2000; Vogel et al. 2001).

The allele frequency of the isoform UGT1A7*3 in our patients was 37.5 % and even higher in the transplanted group (50 %) compared with the published allele frequency of the UGT1A7 gene in caucasians (15.7–36 %). One transplanted patient was homozygous for this isoform. Previous reports demonstrated a reduced enzymatic activity of isoform

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UGT1A7*3 (Guillemette et al. 2000). No poor metabolizer phenotype of CYP2D6 was detected among the patients.

This small sample of patients with kava-kava-induced liver failure may provide a first hint that, in addition to the previously established associations with variants in the CYP2D6 and CYP2C19 genes, polymorphism of the UGT1A7 gene may confer a risk of developing liver toxicity and would warrant attention in larger study cohorts.

References

Guillemette C, Ritter JK, Auyeung DJ, Kessler FK, Housman DE (2000) Structural heterogeneity at the UDP-glucuronosyltransferase 1 locus: functional consequences of three novel missense mutations in the human UGT1A7 gene. Pharmacogenetics 10(7):629–644

Keim V, Bauer N, Teich N, Simon P, Lerch MM, Mössner J (2001) Clinical characterization of patients with hereditary pancreatitis and mutations in the cationic trypsinogen gene. Am J Med 111(8):622–626

Kraft M, Spahn TW, Menzel J, Senninger N, Dietl KH, Herbst H, Domschke W, Lerch MM (2001) Fulminant liver failure after administration of the herbal antidepressant Kava–Kava. Dtsch Med Wochenschr 126:970–972

Stickel F, Shouval D (2015) Hepatotoxicity of herbal and dietary supplements: an update. Arch Toxicol 89(6):851–865. doi:10.1007/s00204-015-1471-3

Vogel A, Kneip S, Barut A et al (2001) Genetic link of hepatocellular carcinoma with polymorphisms of the UDP-glucuronosyltransferase UGT1A7 gene. Gastroenterology 121(5):1136–1144