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Effect of UGT2B7*2 and CYP2C8*4 polymorphisms on diclofenac metabolism

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Highlights

- .UGT2B7*2 shows a strongly reduced activity in diclofenac acyl glucuronidation.
- CYP2C8*4 shows a 35% reduced activity in hydroxylation of diclofenac acyl glucuronide.
- Reduced acyl glucuronidation of diclofenac increases bioactivation to quinonimines.
- Increased bioactivation to quinoneimines may increase risk for diclofenac-induced DILI.

Abstract

The use of diclofenac is associated with rare but severe drug-induced liver injury (DILI) in a very small number of patients. The factors which predispose susceptible patients to hepatotoxicity of diclofenac are still incompletely understood. Formation of protein-reactive metabolites by UDP-glucuronosyl transferases and cytochromes P450 is commonly considered to play an important role, as indicated by the detection of covalent protein adducts and antibodies in the serum of patients suffering from diclofenac-induced liver injury. Since no associations have been found with HLA-alleles, polymorphisms of genes encoding for proteins involved in the disposition of diclofenac may be important. Previous association studies showed that possession of the UGT2B7*2 and CYP2C8*4 alleles is more common in