Get to know a gene: UGT2B15

Summary: UGT2B15 is a pharmacokinetic enzyme that is involved in the metabolism of certain benzodiazepine medications. A common polymorphism, the UGT2B15*2 variant, is associated with reduced activity of the UGT2B15 enzyme and therefore may lead to higher serum levels of certain benzodiazepines.

What is UGT2B15?

The UGT2B15 gene encodes an enzyme responsible for glucuronidation, a phase II metabolic reaction that transforms small lipophilic molecules into water-soluble excretable metabolites. The UGT2B15 enzyme is highly expressed in the liver and mediates the metabolism of a wide range of substrates, including therapeutic medications such as benzodiazepines.[1–3]

Several polymorphisms have been identified in the UGT2B15 gene. One of the best studied is UGT2B15*2, which results in a single G>T substitution, causing an amino acid change at position 85 from aspartic acid (D) to tyrosine (Y).[4] The UGT2B15*2 variant exhibits an allele frequency of approximately 50% in the Caucasian population, and to a slightly lesser extent in Hispanic, African American, Chinese, Japanese, and Korean populations (allele frequencies between 36-49%).[5–8] UGT2B15*2 is associated with decreased glucuronidation and has been shown to be a significant determinant of interindividual variability in the clearance of oxazepam and lorazepam.[1,7] Therefore, this polymorphism may have a significant impact on the metabolism of medications that are substrates of UGT2B15.

Is there a connection between UGT2B15 genotype and benzodiazepine outcomes?

Five studies investigated the effect of UGT2B15*2 on oxazepam metabolism.[1,2,9–11] Two of these studies found that UGT2B15*2 causes a significant decrease in enzyme activity in vitro.[2,9] This is further supported by data from an in vivo study (n=30) that found that carriers of the UGT2B15*2 variant exhibited significantly reduced oxazepam clearance compared to wild-type subjects.[1] In contrast, one study found that UGT2B15*2 significantly increased oxazepam clearance. However, this study used His-tagged UGT proteins, which the authors recognize as a limitation since they may have different enzymatic properties compared to actual UGTs.[11]

The UGT2B15*2 variant has also been shown to affect the metabolism of lorazepam. One in vivo study (n=24) found that homozygous carriers of the UGT2B15*2 variant exhibited a 40-50% lower metabolic activity and systemic clearance of lorazepam compared to wild-type.[7] Consistent with this finding, Court et al. has shown that the UGT2B15*2 polymorphism is associated with reduced glucuronidation of lorazepam, as measured in human liver microsomes.[12]

What is the clinical significance of UGT2B15 genotyping?

Multiple studies have shown that UGT2B15*2 is associated with lower enzyme activity, which could result in elevated plasma concentrations and reduced clearance of medications that are substrates of UGT2B15.[1,2,7,9,12] Additionally, concomitant use of medications that inhibit UGT2B15 can further affect plasma levels and clearance of these medications. For example, valproic acid has been shown to inhibit glucuronidation of UGT2B15 substrates.[3,13] Studies have shown that coadministration of lorazepam and valproic acid reduces the clearance of lorazepam.[14–16] This drug-drug interaction may be clinically significant since it could potentially lead to drug toxicity.[17] The FDA recognizes this and recommends that the dosage of lorazepam should be reduced by approximately 50% when co-administered with valproic acid.[18]

Conclusions

UGT2B15*2 is highly prevalent in the population and has been associated with reduced clearance of therapeutic medications such as oxazepam and lorazepam. Therefore, identifying patients with UGT2B15 polymorphisms may be beneficial to healthcare providers when considering proper dosage and potential adverse effects of medications that are substrates of UGT2B15. Lower doses of UGT2B15 substrates may be required for patients carrying the UGT2B15*2 variant.

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References

1. He, X. et al. Evidence for oxazepam as an in vivo probe of UGT2B15: Oxazepam clearance is reduced by UGT2B15 D85Y polymorphism but unaffected by UGT2B17 deletion. Br. J. Clin. Pharmacol. 68, 721–730 (2009).
2. Court, M. H. et al. UDP-glucuronosyltransferase (UGT) 2B15 pharmacogenetics: UGT2B15 D85Y genotype and gender are major determinants of oxazepam glucuronidation by human liver. J. Pharmacol. Exp. Ther. 310, 656–665 (2004).
3. Uchaipichat, V., Suthisisang, C. & Miners, J. O. The glucuronidation of R- and S-lorazepam: Human liver microsomal kinetics, UDPglucuronosyltransferase enzyme selectivity, and inhibition by drugs. Drug Metab. Dispos. 41, 1273–1284 (2013).
4. Levesque, E., Beaulieu, M., Green, M.D., Tephly, T.R., Belanger, A., Hum, D. W. Isolation and characterization of UGT2B15(Y85): a UDPglucuronosyltransferase encoded by a polymorphic gene. Pharmacogenetics 7, 317–325 (1997).
5. Riedy, M. et al. Genomic organization of the UGT2b gene cluster on human chromosome 4q13. Pharmacogenetics 10, 251–60 (2000).
6. Hwang, M. et al. Genetic Variations in UDP-glucuronosyltransferase 2B7 Gene (UGT2B7) in a Korean Population. Drug Metab. Pharmacokinet. 25, 398–402 (2010).
7. Chung, J. Y. et al. Effect of the UGT2B15 genotype on the pharmacokinetics, pharmacodynamics, and drug interactions of intravenous lorazepam in healthy volunteers. Clin. Pharmacol. Ther. 77, 486–494 (2005).
8. Lampe, J. W., Bigler, J., Bush, A. C., E, U. F. U. D. & Potter, J. D. Prevalence of Polymorphisms in the Human UDP-Glucuronosyltransferase 2B Family : UGT2B4 (D 458 E) , UGT2B7 (H 268 Y) , and UGT2B15 (D 85 Y) Prevalence of Polymorphisms in the Human. Cancer Epidemiol. Biomarkers Prev. 4, 329–333 (2000).
9. Court, M. H. et al. Stereoselective Conjugation of Oxazepam By Human Udp- Glucuronosyltransferases (Ugts): S -Oxazepam Is Glucuronidated By Ugt2B15 , While R -Oxazepam Is Glucuronidated By Ugt2B7 and Ugt1a9 Abstract : 30, 1257–1265 (2002).
10. Liu, W. et al. Genetic factors affecting gene transcription and catalytic activity of UDP-glucuronosyltransferases in human liver. Hum. Mol. Genet. 23, 5558–69 (2014).
11. Nishihara, M., Hiura, Y., Kawaguchi, N., Takahashi, J. & Asahi, S. UDP-glucuronosyltransferase 2B15 (UGT2B15) Is the Major Enzyme Responsible for Sipoglitazar Glucuronidation in Humans: Retrospective Identification of the UGT Isoform by In Vitro Analysis and the Effect of UGT2B15*2 Mutation. Drug Metab. Pharmacokinet. 28, 475–484 (2013).
12. Court, M. H. Isoform-selective probe substrates for in vitro studies of human UDP-glucuronosyltransferases. Methods Enzymol. 400, 104–116 (2005).
13. Ethell, B. T., Anderson, G. D. & Burchell, B. The effect of valproic acid on drug and steroid glucuronidation by expressed human UDPglucuronosyltransferases. 65, 1441–1449 (2003).
14. Chung, J.-Y. et al. Pharmacokinetic and pharmacodynamic interaction of lorazepam and valproic acid in relation to UGT2B7 genetic polymorphism in healthy subjects. Clin. Pharmacol. Ther. 83, 595–600 (2008).
15. Samara, E. E., Granneman, R. G., Witt, G. F. & Cavanaugh, J. H. Effect of valproate on the pharmacokinetics and pharmacodynamics of lorazepam. J. Clin. Pharmacol. 37, 442–450 (1997).
16. Anderson, G.D., Gidal, B.E., Kantor, E.D., Wilensky, A. J. Lorazepam-Valproate Interaction: Studies in Normal Subjects and Isolated Perfused Rat Liver. Epilepsia 35, 221–225 (1994).
17. Lee, S.-A., Lee, J. K. & Heo, K. Coma probably induced by lorazepam-valproate interaction. Seizure 11, 124–5 (2002).
18. FDA Label. Ativan (lorazepam) tablets. (2007).