Clinical validation in a larger patient cohort. Although our results need further patient variation in CBZ pharmacokinetics and might contribute to indicate that SNPs within CBZ pathway genes contribute to inter-patient variation in CBZ pharmacokinetics and CBZ response. We used a pathway-driven approach to evaluate association of genetic variants in major genes involved in CBZ metabolism with its pharmacokinetics in 90 epilepsy patients. Of 25 SNPs analyzed, CYP3A4*1B SNP was significantly associated with CBZ clearance. Significant association of EPHX1 SNPs was observed with greater CBZ-diol/CBZ-epoxide ratios. Among drug transporters, ABCB1 and ABCC2 SNPs were significantly associated with altered CBZ clearance. The results from our study indicate that SNPs within CBZ pathway genes contribute to inter-patient variation in CBZ pharmacokinetics and might contribute to pharmacoresistant epilepsy. Although our results need further clinical validation in a larger patient cohort.

OBJECTIVE

To evaluate association of genetic variants in major genes involved in CBZ metabolism with its pharmacokinetics in epilepsy patients.

METHODS

STUDY DESIGN

90 epileptic patients on CBZ maintenance therapy and received an intravenous stable-labeled CBZ formulation

Association of SNPs within drug transporters ABCB1 and ABCC2 with CBZ PK

Association of SNPs in (A) nuclear hormone receptor PXR and (B) Phase II enzyme UGT2B7 with CBZ PK

Overall summary of SNP associations with CBZ PK endpoints

CONCLUSIONS

- SNP within CBZ pathway genes contribute to inter-patient variation in CBZ pharmacokinetics and might contribute to pharmacoresistant epilepsy.
- Future studies in larger patient cohorts are required to validate our findings and better understand clinical implication of CBZ pharmacogenomics.

ACKNOWLEDGEMENTS

This study was supported in part by grants from the National Institutes of Health (1K01NS050309-03, 1K01NS050309-04, 1K01NS050309-05, and K01NS050309-06). The authors thank the patients who participated in this study. We would like to acknowledge Dr. William Leppik for assistance in DNA isolation, BioMedical Genomics Center (BMGC) for genotyping facility and Minnesota PUMA-Institute of Personalized Medicine (PUMA-IIPM) for assistance in data analysis.

90th North American ISSX Meeting