Influence of CYP2B6 and CYP2C19 Phenotypes on Sertraline Exposure in Children and Adolescents

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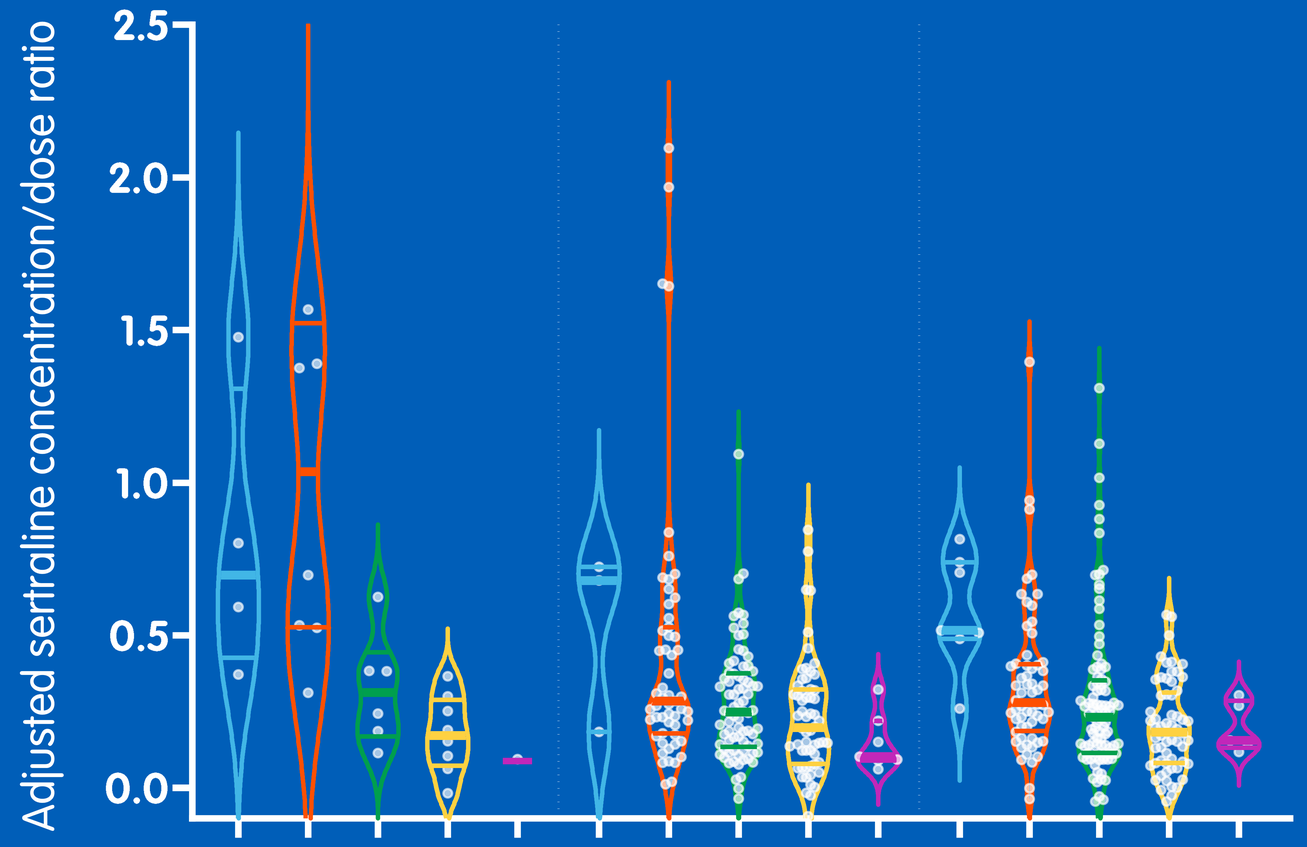
Objective

To determine how CYP2B6 influences pharmacokinetics of sertraline in pediatric patients

Methods

Remnant plasma samples were collected from 508 pediatric patients aged 5-18 years who received sertraline within the prior 24h. Sertraline was measured by LCMS either at the UCSD or Indiana University. Pharmacogenetic testing was performed as part of routine care. Using the Agena MassARRAY system, eight CYP2C19 alleles were tested (*2, *3, *4, *5, *6, *7, *8, *17). Two CYP2B6 alleles were tested in a subset of 462 patients (*6, decreased function; and *18, no function). Using linear regression in R, the log-transformed dose-normalized concentration was tested for associations with age, sex, weight, race, ethnicity, CYP2C19 phenotype, CYP2B6 phenotype, assay site, and time since the last dose.

Slower CYP2C19 and CYP2B6 metabolizers may benefit from dose reductions or slower titration of sertraline



Sertraline concentration was adjusted for time after dose, with the model residuals plus the median concentration/dose for the population are plotted. One data point with a value of 6.2 is excluded from the graph for a CYP2C19 IM CYP2B6 IM. PM, poor metabolizer; IM, intermediate metabolizer; NM, normal metabolizer; RM, rapid metabolizer; UM, ultrarapid metabolizer.

Discussion

This is the first study to evaluate the combined effect of CYP2C19 and CYP2B6 phenotypes on sertraline exposure in pediatric patients. The dose-normalized concentration was highest among CYP2C19 poor and intermediate metabolizers that were also CYP2B6 poor metabolizers, which is similar to adults. CYP2C19, CYP2B6, weight and time after dose explained 17.5% of the variability in dose-normalized sertraline concentration. These results support the Clinical Pharmacogenetics Implementation Consortium recommendations for CYP2C19- and CYP2B6-related reductions in sertraline dose or slower titration.

Acknowledgements

We are thankful for the efforts of Jada Bouyer, Kynnedi Williams, and Ashley Sarbell for sample collection, the Molecular Genetics Lab at Cincinnati Children's Hospital Medical Center for data extraction, the MPRINT and the Cincinnati Children's Center for Pediatric Genomics for funding.

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