K58 Fluoxetine Toxicity — Pharmacogenomics, Drug Interactions, and Dosage Converge to Create the Perfect Storm: A Case Report

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After attending this presentation, attendees will better understand the importance of contributing factors to toxic concentrations of fluoxetine, such as polymorphism of metabolizing enzymes, drug interactions, and drug dosage.

This presentation will impact the forensic science community by providing toxicologists, pathologists, and the medical community with an increased awareness of pharmacogenomics as plausible causes contributing to lethal drug levels, especially in conjunction with drugs taken concomitantly at high dosages.

Introduction: An 18-year-old, non-verbal, White male diagnosed with autism was found dead in his room. Lethal levels of fluoxetine were found in the blood. The medical examiner believed the deceased may have ingested the fluoxetine intentionally. Investigation revealed the parents of the young man administered the correct amount of medication. They believed the capsules may have been the wrong strength.

Method: The capsules were analyzed and found to contain the correct dosage of fluoxetine. Based upon the high levels of fluoxetine found in the blood and liver, pharmacogenomics testing was performed. The postmortem blood was extracted, purified, and genotyped. The amplicon-based targeted sequencing method was chosen to achieve results. Targeted regions were amplified using a SmartChip Polymerase Chain Reaction (PCR) system and sequenced in parallel with deep coverage on MiSeq® platform. The sensitivity and specificity of this test is 100% and 100%, respectively. This panel includes 25 genes and 196 variants based on the Food and Drug Administration's (FDA's) work group guidance and the recommendations of the Clinical Pharmacogenetics Implementation Consortium (CPIC) and Dutch Pharmacogenetics Working Group (DPWG). Further investigation revealed the patient was prescribed and taking 80mg of fluoxetine per day, 6mg of risperidone per day, and 50mg of topiramate per day.

Results: The capsules were assayed and found to contain 20mg of fluoxetine per capsule. Toxicological findings revealed initial blood screen, fluoxetine 6.4 micrograms/mL. Quantitation of chest blood revealed fluoxetine 4.0 micrograms/mL. Quantitation of liver yielded greater than 160 micrograms/gram. Pharmacogenomic testing revealed the genotype of CYP2D6 *1/*4, phenotype of an intermediate metabolizer. The variant found was an intermediate metabolizer of fluoxetine.

Conclusions: Review of all three variables suggested that they had all contributed to the fluoxetine intoxication. The deceased intermediate metabolizer phenotype along with concomitant administration of another substrate, risperidone, combined with a high dose of fluoxetine created the perfect storm, resulting in the demise of the individual from fatal concentrations of fluoxetine. The patient had CYP2D6 intermediate metabolizer phenotype, which slowed down the metabolism of fluoxetine, thus resulting in a high concentration of fluoxetine in the blood. This high concentration, combined with risperidone, a known inhibitor of CYP2D6, further compromised the metabolism of fluoxetine. All of these variables converged into the perfect storm of toxicity. The medical examiner ruled the cause of death fluoxetine intoxication and the manner of death undetermined.

Pharmacogenomics, Drug Interactions, Fluoxetine

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