H135 Forensic Applications of Postmortem Pharmacogenomics

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After attending this presentation, attendees will better appreciate the role of pharmacogenomics testing in the investigation of potential drug-related deaths.

This presentation will impact the forensic science community by promoting the use of pharmacogenomics testing as an adjunct to postmortem drug testing in drug-related deaths to help avoid erroneous certifications of death.

Case 1: A 57-year-old male was found dead in his cell at the Center for Forensic Psychiatry. He was initially asystolic and in cardiac arrest and was pronounced dead shortly after arrival at the emergency room. His past medical history was significant for: hypertension, hyperlipidemia, hypothyroidism, diabetes, alcoholism, depression, schizophrenia, and polydipsia (excessive thirst). His drug count was accurate.

An autopsy demonstrated an abrasion on the submental region. Examination of the anterior portion of the spine revealed an acute fracture and hemorrhage overlying the C6-C7 intervertebral space.

Postmortem toxicological analysis using Liquid Chromatography/Tandem Mass Spectrometry (LC/MS/MS) revealed elevated levels of tramadol 3,000ng/mL and the O-desmethyltramadol metabolite at 100ng/mL in iliac blood. The clozapine concentration was 1,100ng/mL and its metabolite, norclozapine, at 680ng/mL in iliac blood. Both drugs were at potentially toxic concentrations. In consideration of the circumstances, autopsy, and toxicology findings, the cause of death was certified as tramadol and clozapine toxicity.

Postmortem genetic testing using Sanger sequencing revealed a heterozygous CYP2D6*4 genotype and indicated that one copy of the CYP2D6 was inactive. This could explain the increased concentration of clozapine, although it is thought that CYP1A2 and 3A4 are responsible for the metabolism of this drug. Tramadol is metabolized by 2D6, 2B6, and 3A4 CYP450 enzymes.

Case 2: An 80-year-old female was admitted to the hospital for biopsy of a pelvic mass. She had a past medical history significant for Chronic Obstructive Pulmonary Disease (COPD), asthma, and arthritis. She was depressed over the new diagnosis of rectal cancer. She was discharged to a nursing home five days later for elder care. Tramadol 50mg/q6 and nortripyline 100mg @ hs were added to her discharge medications.

An autopsy demonstrated a metastatic vagina carcinoma and severe coronary atherosclerosis. Toxicology analysis revealed acetaminophen 120mcg/mL (12-20ug/ml) via High-Performance Liquid Chromatography (HPLC), tramadol 46,000ng/mL, O-desmethyltramadol 500ng/mL (420-720ng/ml) by (LC/MS/MS), nortriptyline 3,800ng/mL (170-380ng/ml) by Gas Chromatography (GC), mirtazapine 240ng/mL (137-225ng/ml) by GC.

Toxicology revealed markedly high levels of tramadol and nortriptyline. The decedent underwent genetic testing using Multiplex Polymerase Chain Reaction (PCR) and Multiplex Allele Specific Extension (ASPE) for CYP2D6 genotype to investigate her ability to metabolize tramadol, nortriptyline, and other drugs. The patient had homozygous mutations, carried two non-functional CYP2D6 alleles, and was a poor metabolizer of tramadol and nortriptyline. The cause of death was certified as tramadol and nortriptyline toxicity due to CYP2D6 poor metabolizer status. The manner of death was accident.

Pharmacogenomics is the study of an individual's genotype and their ability to metabolize foreign compounds.

There are some 50 distinct CYP450 enzymes. CYP2D6, CYP2C9, CYPC19, and CYP2D6 account for 75% of drug metabolism by P450 enzymes. Mutations of CYP450 enzymes can result in elevations and decreases in parent drugs and their more potent metabolites: (1) ultrarapid metabolizers: — multiple copies of a gene results in elevated metabolites; (2) extensive metabolizers (wild-type) — single copy of a gene with normal activity; (3) intermediate metabolizers (heterozygotes) — exhibit decreased enzymatic activity; and (4) poor metabolizers (homozygotes/*double heterozygotes*) — have no detectable activity.[1]

Medical examiners and coroners are just beginning to appreciate the role that pharmacogenomics can play as an adjunct for drug death certification. Previous studies have demonstrated the high prevalence of CYP2D6 genetic variations corresponding to intermediate and slow metabolizers.[2]

Death investigators should consider pharmacogenomic testing in the following situations: (1) excessive drug concentrations not consistent with prescribed dosages; (2) deaths occurring shortly after starting a new medication; (3) elevated drug concentrations with diminished or absent metabolites; and, (4) elevated drug concentrations without confirmed history of intentional administration.

Pharmacogenomics has demonstrated a promising role in the interpretation of drug-related toxicity and sensitivity.[3,4]

Reference(s):

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Pharmacogenomics, Molecular Autopsy, Drug-Related Deaths