The Application of Forensic Toxicology as a Multidisciplinary Research Field

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Abstract

Pharmacogenetics examines how various DNA genes behave on their own following drug delivery. Due to advancements in molecular genetics and genome sequencing methods, pharmacogenetic research has been carried out recently. In addition to serving medical needs, pharmacogenetics can be a useful tool for post-mortem toxicological data interpretation clarification, which is frequently essential for identifying the cause and manner of death. In addition to bringing pharmacogenetics to the attention of the forensic community, the aim of this systematic literature review is to provide a workflow that forensic toxicologists might employ when determining the cause of death in situations involving drug use or misuse. This study shows how the scientific community is required to put in a lot of effort to provide evidence in forensic practise, showing how this investigation might become a crucial tool both in civil and forensic contexts. The search engine utilised the following keywords: (pharmacogenetics) AND (forensic toxicology); (pharmacogenetics) AND (post-mortem); (pharmacogenetics) AND (forensic science); and (autopsy). 125 items in all were gathered. This systematic review covered 29 of these papers. 25% of the included studies were case reports (n = 7), while 7 out of 21 total research were original papers. Codeine, morphine, and methadone were the medications that had been investigated the most, followed by antidepressants (tricyclic antidepressants and venlafaxine). Additionally, all studies emphasised the significance of a pharmacogenetics research in drug-related mortality, particularly in situations when drugs of abuse were not overdosed. This study emphasises the value of forensic pharmacogenetics, a branch of toxicology that is currently little understood but is very useful in situations of sudden death, overdose deaths, drug-related deaths, and complaints of medical misconduct.

Keywords: Colorectal cancer • Colorectal liver metastasis • Biomarker

Introduction

The principles of various disciplines, including chemistry, physics, and biology, are used in forensic science to provide the alleged "weight of evidence." The forensic toxicology laboratory seeks to identify and measure the presence of drugs and other chemicals in bodily fluids collected during autopsies in this multidisciplinary context. Additionally, a toxicological investigation could be carried out for medical and legal reasons (i.e., drug and alcohol tests for commercial driver licencing or involving occupational medicine due to the consequences of workers exposed to toxic substances). Since pharmacokinetics, pharmacodynamics, and ultimately the bioavailability of a drug are influenced by a genetic substrate, it is crucial to comprehend the critical role of pharmacogenetics in forensic toxicology. In forensic pathology, the findings of the crime scene investigation, anamnesis, autopsy, and toxicological data guarantee the identification of the cause of death. Pharmacogenetics may be useful in this situation to resolve toxicological conundrums, particularly in suicide, accident, and death from unexplained causes situations. When assessing the post-mortem concentration of a substance in body fluids or organs, one should also take into account the potential impact of pharmacogenetics on drug metabolism. Pharmacogenetics is a word that is frequently used to refer to the study of inter-individual changes in DNA sequence that may have an impact on a drug's pharmacokinetics or pharmacodynamics. The genes that code for transporter proteins and enzymes that metabolise medicines, receptors, etc. may be impacted by these changes. Pharmacogenetics aims to assess the effects of a medicine and anticipate how each individual will react to it. Pharmacogenetics is used in clinical practise to evaluate a patient's or a group of patients' potential to either produce the intended benefit or, conversely, to develop unfavourable consequences. The advancement of genome sequencing methods and molecular genetics has allowed for the implementation of pharmacogenetic research in recent years. Finding disease-specific genes and gene products as well as allelic variations that affect treatment response are two of the most important applications of pharmacogenetic research in medicine.

Additionally, pharmacogenetics might be a useful tool for elucidating how toxicological data is interpreted in post-mortem investigations, which is sometimes essential for determining the cause and manner of death. In fact, forensic pathologists are frequently held accountable for fatalities brought on by the use or abuse of drugs and narcotics. The CYP2D6 gene, for instance, is implicated in the metabolism of several medications, including morphine and its derivatives (codeine, tramadol, dihydrocodeine, and oxycodone), and some CYP2D6 polymorphisms can lower methadone clearance. The metabolism of benzodiazepines and buprenorphine is instead regulated by CYP3A4. In situations of mortality linked to a suspected drug overdose, evaluating the presence of cytochrome inducing or suppressing mutations can offer insights. In addition to bringing pharmacogenetics to the attention of the forensic community, the aim of this systematic literature review is to lay out a process that forensic toxicologists can employ when there are drug-related deaths with unexplained causes of death. use/abuse. This study shows how the scientific community is required to put in a lot of effort to provide evidence in forensic practise, showing how this investigation might become a crucial tool both in civil and forensic contexts.

Forensic pharmacogenetics is a branch of toxicology that examines the genotypes and allelic variations of genes that code for drugs-metabolizing enzymes. According to the findings of this review, one of the most researched genes is CYP2D6, which produces an enzyme that belongs to the cytochrome P450 superfamily. Ultra-rapid metabolizers (UM), extensive metabolizers (EM), poor metabolizers (PM), lacking functional enzymes due to defective or deleted relative genes, and intermediate metabolizers (IM), carrying alleles that partially decrease enzyme activity, are the four main phenotypes caused by genetic polymorphisms of the CYP2D6 gene. 7% of those who died from an opioid overdose had an ultra-rapid phenotype, which amplified the toxic effect, according to a recent review [59]. In fact, it is essential for the metabolism of the endocannabinoids arachidonoylethanolamide (anandamide), 20-hydroxyeicosatetraenoic acid ethanolamide (20-HETE-EA), 8,9-, 11,12, and 14,15-epoxyeicosatrienoic acid ethanolamides (EpETrEEAs), which may influence the signalling of the endocannabinoid system. It is well known that this gene's polymorphisms may affect how fatty acids, steroids, and retinoids are metabolised. Additionally, it has been shown to play a role in the oxidative metabolism of medications such adrenoceptor antagonists, antiarrhythmics, and tricyclic antidepressants. The CYP2D6 gene, along with all CYP class enzymes, is in charge of the liver phase I metabolism of pharmaceuticals and foreign substances.

The phase II enzymes (such as UDP glucuronosyltransferase and N-acetyltransferase) conjugate electrophilic intermediates produced by the

P450 family, which are then eliminated. Although there are at least 60 P450 genes, the most researched subgroups are CYP1A2, CYP2A6, CYP2B6, CYP2C19, CYP2D6, CYP2E1, and CYP3A4, which are in charge of processing the bulk of prescription and over-the-counter medications. This enzyme has medical and legal implications in light of the available evidence. Additionally, certain antidepressants, such as nortriptyline, can become more toxic and have severe adverse effects when they are present with CYP2D6 enzymes that metabolise quickly or ultra-quickly. The forensic community may therefore find it highly useful to comprehend the CYP2D6 haplotype information of all metabolizer phenotypes. Indeed, to examine the cause and/or modality of death in a number of medico-legal instances, Koren et al. and Koski et al. undertook targeted CYP2D6 genotyping of specific deaths. Furthermore, the CYP2D6 genotyping instance reported by Koren et al. was a prime illustration of the ultra-rapid conversion of codeine to morphine, which exacerbated toxicity and led to the subject's demise. In these situations, the research of CYP enzyme cytochromes is crucial. Additionally, these enzymes are expressed in other cells, including those of the central nervous system, in addition to the liver (CNS). The CYP2C19 and CYP3A4 genes are routinely examined in order to assess the potential influence of the genetic predisposition and the cause of mortality. These results are consistent with those stated in this systematic review. Certainly, Shen M. et al. confirmed that the *18 CYP3A4 and *2 CYP2C19 alleles were linked to poor metabolism, increasing the drug's toxicity in a trial of 300 healthy persons given Zolpidem. Drug metabolism is significantly influenced by genetic variables, which has significant consequences for forensic toxicology.

Ciszkowski C. reported that cytochrome P-450 2D6 (CYP2D6) was genotyped and revealed a functional duplication of the CYP2D6 allele, resulting in an ultrafast metabolizer phenotype in a case study about the death of a healthy 2-year-old boy following codeine and acetaminophen ingestion. Similar findings of abrupt death following codeine administration caused by CYP2D6 genetic polymorphism were published by Koren G. et al. The prescribed dose of codeine was within the safe limits, but the accelerated conversion of codeine to morphine led to a hazardous accumulation of morphine. In a different investigation, doxepin (a tricyclic antidepressant) was administered to a52-year-old woman who later passed away. The blood was analysed using LC-MS.Additionally, Wu A.H. noted that a pharmacogenetic research enabled them to confirm that a young woman who took codeine and caused a car accident was not in a condition of acute intoxication, which element served as support for her release from custody in the case report. There have also been reports of deaths caused by the administration of venlafaxine, rapid drug metabolism with enhanced toxicity, and patient deaths. Another protein involved in how medications that impact the CNS, particularly psychiatric pharmaceuticals, function is called P-gp. These medications, which are expressed by the MDR1 (or ABCB1) gene, bind not just to receptors like the dopamine D2 receptor (D2-R), but also to P-gp and other metabolic enzymes. Population and interindividual differences are crucial in the operation of xenobiotics, psychoactive medicines, and endogenous poisons. According to Neuvonen A.M.'s explanation in the current systematic study, pharmacogenetic investigation employing quantitative real-time PCR revealed a relationship between ABCB1 polymorphisms and higher mortality after analysing 112 deaths caused by digoxin administration, proposing genotyping analysis prior to digoxin treatment. A different study, however, found no evidence of an elevated mortality risk following the MDR1gene pharmacogenetic analysis of P-gp following methadone use. In-depth research is required to determine P-significance gp's in forensic toxicology. The p11 protein (also known as S100A10), which is a critical player in the dynamic modulation of serotonin and has been linked to both major depressive disorder (MDD) and the effectiveness of antidepressant medications, is another protein under investigation in pharmacogenetics. There has been evidence that some p11 genotypes are less responsive to antidepressant medication, leading to an increase in suicides. Future toxicological research may be able to shed more light on this issue in suicide cases as there are no studies analysing the significance of this protein in forensic toxicology in the current systematic review. According to Budowle et al., unexpected, inexplicable suicides or fatalities linked to chronic or acute pharmacological therapy, including abrupt cardiac deaths, should be investigated using genetic variation analysis and its implications on metabolism.

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