The Research of Medical Science Review
ISSN: 3007-1208 & 3007-1216 Volume 3, Issue 4, 2025

A NARRATIVE REVIEW ON FORENSIC PHARMACOKINETICS AND ITS SCOPE

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DOI:https://doi.org/10.5281/zenodo.15267928

Keywords
Forensic; pharmacokinetics; legal; genetic-variability; drug-interaction.

Article History
Received on 13 March 2025
Accepted on 13 April 2025
Published on 23 April 2025

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Abstract

Background: *Forensic pharmacokinetics refers to the study of the absorption, distribution, metabolism, and excretion of drugs and other chemical substances that can be used for criminal activities in a legal context. Forensic drug pharmacokinetics face several challenges related to individual variability and the complexities of postmortem drug analysis.*

Objective: *Objective of the current review is to provide a comprehensive overview of all literature related to implications and significance of forensic pharmacokinetics to promote the implication of forensic pharmacokinetics in legal investigation.*

Methods: *Research studies were collected by diversified authentic search engines including: Google Scholar, PubMed, Elsevier, Science Direct, and Springer. The studies that were published during the time span of 2015-2024 were included in the study. Studies were selected, screened and included in the review as per PRISMA. Quality of literature was assessed by Grading of Recommendation Assessment, Development and Evaluation.*

Results: *Findings revealed intoxication accidental or intentional for the cannabiniods, cocaine, benzodiazepines, opioids, methamphetamines, alcohol, ketamine, methadone, anti-depressants and anti-psychotics. Drugs were detected in post-mortem in blood, body fluids, hairs, nails and bones even several months/years' post death. However, pharmacogenomics, inter-individual differences in drug metabolism, and genetic variability plays a critical role in forensic investigations.*

Conclusion:*Forensic pharmacokinetics plays imperative role in determining intoxication timelines, identifying death causes and linking substance use to criminal behavior. Genetic variability, inter-individual variability, drug interaction, intoxication timelines influence investigations.*

INTRODUCTION

Forensic pharmacokinetics (PKs) refers to the study of the absorption, distribution, metabolism, and excretion (ADME) of drugs and other chemical substances that can be used for criminal activities in

a legal context. It plays a critical role in forensic science by serving to regulate the timing and quantity of drug intake, which is essential in both civil and criminal investigations.[1] Considering drug PKs; it permit forensic experts to discriminate between acute and chronic exposure, evaluate impairment levels, discover potential overdoses, and assess the time of drug administration. This data is crucial in cases involving poisoning, drug-facilitated crimes, postmortem toxicology, and impaired driving; the investigation provides crucial evidence for legal proceedings to establish the facts in a legal proceeding. Forensic PKs bridges pharmacology with the legal system, ensuring that the interpretation of drug-related evidence is accurate, scientifically sound, and legally admissible.[2]

Historical Context of Forensic Kinetics:
Forensic PKs in legal investigations has its roots in the comprehensive history of forensic science, which dates back to ancient evolutions like Greece and Rome. Primary toxicological studies in these civilizations laid the groundwork for the effects of drugs and poisons in postmortem inspections. As forensic science advanced, procedures such as autopsies and the detection of toxins gained prominence, with notable advancements like the chemical exposure of arsenic by Carl Wilhelm Scheele in the 18th century.[3] One notable case is the use of forensic pharmacokinetic (PK) in determining the lethal dose of propofol in Michael Jackson's death, which helped to convict his physician.[4]

Basic principles of drug pharmacokinetics:
Optimizing therapy necessitates precise data analysis and parameter approximation to interpret these processes, principally in critically ill patients where physiological changes may affect drug PKs. Additionally, pharmacodynamics (PDs) indices help tailor dosing for specific antibiotic classes, enhancing treatment outcomes.[5] In the domain of Database Forensic Investigation (DBFI), existing models show redundancy and lack unified approaches.[6, 7] Solutions include developing generic DBFI models, a semantic metamodeling language, and a knowledge repository to better structure and share DBFI processes. These processes are critical for ensuring accuracy, preserving evidence integrity, and improving outcomes in forensic investigations.[6, 8]

Applications of Forensic PKs:
The knowledge is instrumental in reconstructing events leading to an overdose or impaired state. For example, an understanding the shift from first-order to zero-order kinetics; where the metabolism rate saturates and leads to accumulation; which helps in identifying overdose scenarios, as seen with substances like aspirin and ethanol.[7, 9] It enables forensic scientists to discern whether a drug overdose or specific drug impairment contributed to death. Overall, the application of forensic PKs is vital for accurate drug-related investigations, providing clarity on drug dosages, effects, and their role in both fatal and non-fatal incidents.[10-12]

Challenges of Forensic PKs:
Forensic drug PKs face several challenges related to individual variability and the complexities of postmortem drug analysis. Individual factors such as age, genetics, and disease states significantly impact PKs, leading to variability in how drugs are absorbed, distributed, metabolized, and eliminated. This variability complicates the interpretation of forensic drug data because it affects the drug concentrations found in different individuals.[13-15] Analyzing postmortem drug levels presents its own set of difficulties. Postmortem redistribution; where drugs shift from one part of the body to another after death can lead to misleading results about the actual drug concentrations present at the time of death.[16] Biochemical changes and decomposition processes further complicate these analyses. Therefore, while blood from peripheral vessels is generally preferred for accurate quantitative analyses, alternative matrices like vitreous humor may be used when blood is unavailable. These challenges highlight the need for meticulous forensic practices and the consideration of multiple factors to accurately interpret drug-related findings in forensic cases.[13, 17-19]

Techniques employed for forensic PKs evaluation:
The techniques used in forensic PKs for the evaluation of different cases are Gas-Chromatography Mass-Spectrometry (GC-MS) for

the detection of illicit drugs, poisons, and therapeutic agents in biological samples (blood, urine, hair); Liquid-Chromatography Mass-Spectrometry (LC-MS) for the analysis of opioids, benzodiazepines, and new psychoactive substances; High Performance Liquid-Chromatography (HPLC) for the analysis of pharmaceutical drugs, poisons, and biological samples (blood, urine, tissues); Fourier-Transform Infrared Spectroscopy (FTIR) for the identification of unknown drug powders, pills, or related materials; Thin-Layer Chromatography (TLC) for the preliminary drug testing in biological fluids, used in forensic labs with limited resources; Headspace Gas Chromatography (HS-GC) used primarily for blood alcohol content (BAC) analysis and volatile substance detection in DUI cases; immunoassays for rapid drug screening in urine or blood, workplace testing, roadside drug testing; Capillary Electrophoresis (CE) for drug analysis, DNA profiling, separation of charged molecules in forensic samples; Scanning Electron Microscopy (SEM) with Energy-Dispersive X-ray Spectroscopy (EDS) for gunshot residue analysis, fiber analysis, trace evidence detection; Hair and Nail Analysis for the cases involving chronic drug use or poisoning, providing a longer detection window compared to blood/urine tests; autopsy and histopathology used to examine tissue damage and drug toxicity in overdose-related fatalities and DNA Analysis (Forensic Genomics) used in drug-facilitated crimes (e.g., sexual assault) to match DNA evidence with suspects.[20, 21]

Objective of the current review:

The main objective of the current review is to provide a comprehensive overview of all literature related to implications and significance of forensic PKs. The review may also promotes the implication of forensic PKs in legal investigation and explore the use of different advanced tools utilized in the facilitation of criminal investigation.

METHODOLOGY

Study Design:

This literature review intends to provide a comprehensive outline of forensic PKs. The findings from different studies were taken and reviewed to draw a meaningful conclusion and summarize knowledge from different research platform. The review seeks to enhance understanding of the PK and its implication in forensic utilization of different drugs.

Data Collection: The research study comprises a literature review, for this purpose the collected data of different research articles were searched through diverse authentic search engines, including: Google Scholar, PubMed, Elsevier, Science Direct, and Springer. The studies that were published during the time span of 2015-2024 were included in the study. Procedure of articles selection, screening and inclusion in the review has been shown by PRISMA flow diagram (Figure 1).[22]

Quality of literature:

The criteria applied for establishing quality of literature is GRADE (Grading of Recommendation Assessment, Development and Evaluation).[23]

Inclusion and Exclusion Criteria:

- The articles that were latest and published during the time span of last 10 years, and represent the PKs of drug utilization and its techniques in forensics, while the studies which had different prime objectives were excluded.
- Articles that were in English, studies from other language were excluded.

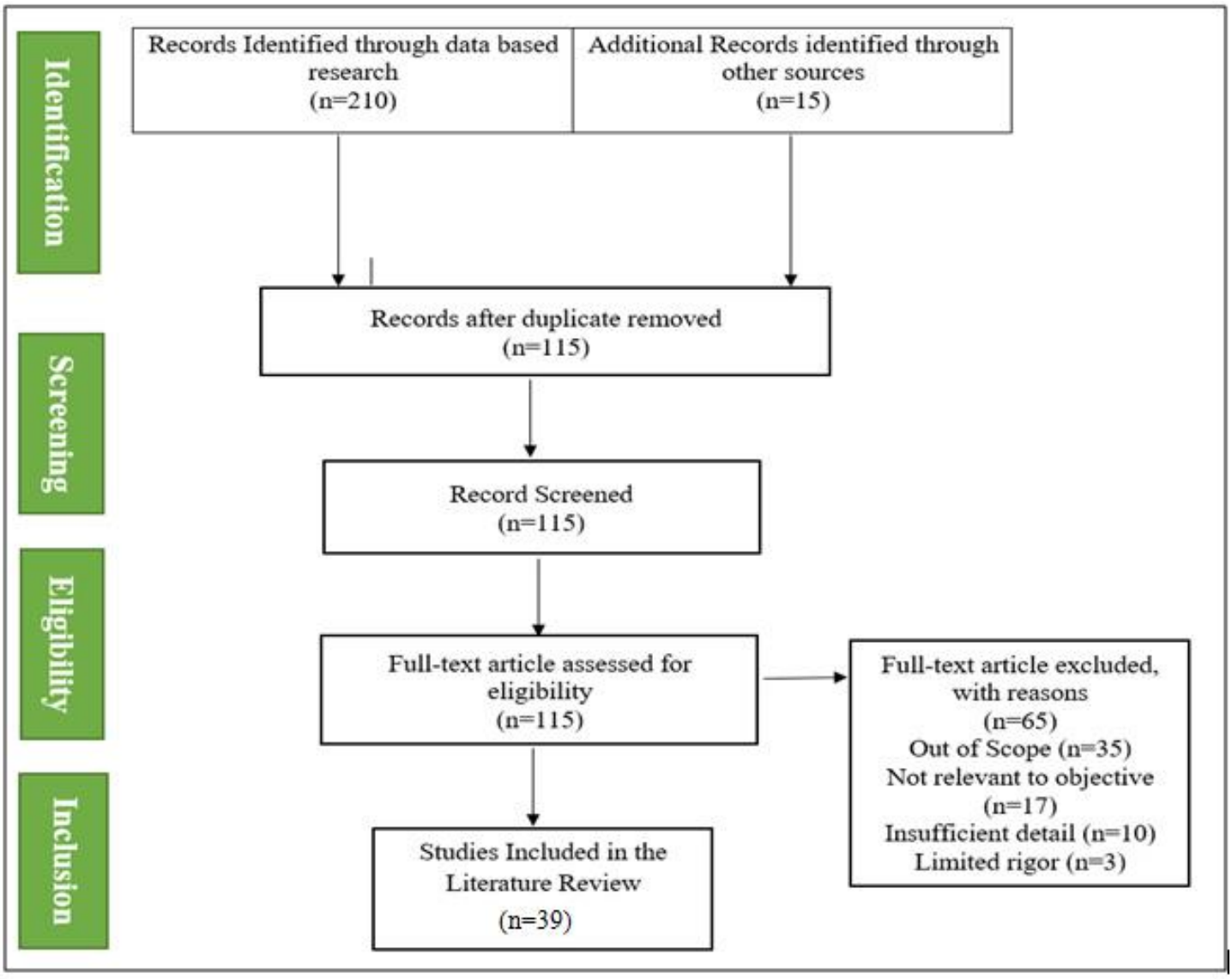

Figure 1: PRISMA diagram; selection of different article for the review

RESULTS

Table 1: The case studies and forensic investigations related to synthetic cannabinoids and other substances, highlighting PK data and its relevance to determining the timeline or cause of death.

Case Study	Substance	PK Data	Forensic Findings	Link to Timeline or Cause of Death	References
MAM-2201 Intoxication	MAM-2201	Blood level: 49 ng/ml (1 hour post-smoking)	Acute transient psychotic state with agitation, aggression, anxiety, vomiting; sympathomimetic syndrome	The concentration of MAM-2201 in blood shortly after smoking helps establish the timeline of intoxication and symptoms onset.	[17, 24-26]
AM-694 Detection	AM-694	Urine level: 0.084 µg/L; Blood levels of midazolam and α-hydroxymidazolam	Presence of AM-694 and benzodiazepines; ingestion of an unknown pill and alcohol	AM-694 detection in urine and blood aids in confirming substance abuse and potential cause of intoxication-related trauma.	
Synthetic Cannabinoids Intoxication	5F-ADB, MMB-2201	No specific PK data provided	Cases of altered mental status, tachycardia, loss of consciousness	The presence of synthetic cannabinoids confirms the cause of acute intoxication and relates to symptoms and overdose severity.	
Ketamine Elimination	Ketamine	Hair concentration: 58 pg/mg (4 months post-treatment); 67 pg/mg (17 weeks post-treatment)	Ketamine detectable in hair segments for up to 4 months after cessation	The decline in Ketamine concentration in hair provides insights into the drug's elimination timeline and supports the interpretation of past drug use.	

Table 2: Comparative analysis of the pharmacokinetic (PK) profiles of various drugs of abuse, highlighting how these profiles impact forensic interpretation

Study	Drug/Substance	Matrix	PK Profile (Metabolism/Clearance)	Metabolite Patterns	Forensic Significance	References
Bio sampling strategies for emerging drugs of abuse	Synthetic cannabinoids, cathinones, phenethylamines	Blood, oral fluid, hair	Varies greatly depending on the class of drug. Synthetic cannabinoids show slower clearance rates in hair; phenethylamines have a faster clearance rate in blood.	Synthetic cannabinoids (THC) produce hydroxylated metabolites; phenethylamines produce amphetamine-like metabolites	Synthetic cannabinoids' long retention in hair makes them suitable for long-term abuse detection, while blood is more suited for recent usage.	[27-30]
Postmortem protein stability of CYP enzymes (CYP1A2, CYP3A4)	General drugs metabolized by CYP enzymes (e.g., opioids, benzodiazepines)	Liver (post-mortem)	CYP enzyme activity is severely decreased in post-mortem tissue; however, protein levels are stable under certain conditions (e.g., storage at 4°C).	Specific drug-metabolizing enzymes such as CYP1A2 and CYP3A4 show varying patterns depending on post-mortem decay.	Post-mortem CYP protein levels can provide information about metabolism rates before death, aiding in determining cause of death in toxicology cases.	
High-resolution	Various drugs of	Blood,	Alcohol has a fast clearance rate	Alcohol produces	Alcohol's rapid clearance limits	

mass spectrometry in toxicology	abuse (e.g., alcohol, opioids, benzodiazepines)	urine, hair	(hours); opioids show rapid metabolism and produce glucuronide metabolites; benzodiazepines have longer half-lives with active metabolites.	acetaldehyde and acetate; opioids are metabolized into morphine and other glucuronide metabolites; benzodiazepines are metabolized into nordiazepam.	detection windows in blood/urine, while opioids and benzodiazepines are detectable for longer periods due to slow metabolism or active metabolites.	
Waste-water analysis in forensic intelligence	Methamphetamine, cocaine, MDMA (3,4-Methylenedioxy methamphetamine)	Waste-water	Methamphetamine has a long half-life (~12 hours), cocaine is rapidly metabolized (~1 hour half-life), and MDMA has an intermediate half-life (~7 hours).	Methamphetamine metabolites are excreted in urine unchanged (~30%); cocaine is metabolized into benzoylecgonine, ecgonine methyl ester; MDMA is metabolized into MDA.	Methamphetamine's slower clearance allows it to accumulate in waste-water, indicating widespread use over time. Cocaine's rapid clearance suggests recent use, as it is quickly converted to metabolites.	

Table 3: Findings from the eight cases of drug-related deaths based on postmortem examination, toxicology results, and the cause and manner of death

Case No.	Age / Gender	History	Postmortem Findings	Toxicology Results	Cause of Death	Manner of Death	References
1	52/M	Opioid, cocaine abuse, alcohol use	Liquid in airways, lung edema, no traumatic lesions, alveolar hemorrhage, emphysema	Positive for opioids, cocaine, alcohol (0.44 g/L), lor-metazepam	Respiratory failure due to opioids and benzodiazepines with cocaine/alcohol	Accidental	[31-36]
2	41/M	Illicit drug use, recent rehab	Pulmonary hemorrhages, cerebral edema, injection marks, petechial hemorrhages in heart and lungs	Positive for opioids, cocaine, THC	Respiratory failure due to "speedball" (cocaine and opioids) co-assumption	Accidental	
3	66/F	Depression, alcoholism, psychiatric disorders	Acute emphysema, brain edema, no trauma or aggression signs	Positive for benzodiazepines, high lor-metazepam concentrations, alcohol (1.01 g/L)	Asphyxia by suffocation after alcohol and benzodiazepines intake	Suicide	
4	21/M	Opioid, cocaine abuse	Brain and lung edema, multiple injection marks,	Positive for opioids, cocaine, cannabis metabolites	Cardio-respiratory failure due to opioid	Accidental	

			no trauma		overdose and cocaine co-assumption	
5	16/F	Illicit drug use, methadone in house	Pulmonary edema, myocardial fibrosis, stasis, injection marks	Positive for methadone, cocaine, THC, opioids, high methadone concentration	Respiratory failure due to methadone overdose, heroin intoxication, cocaine	Accidental
6	54/M	Cocaine, heroin, methadone abuse, suicide attempts	Cyanosis, lung foam, hemorrhagic petechiae, no trauma, methadone therapy	Positive for methadone in blood, urine, liver, brain, and bile	Respiratory failure due to methadone overdose	Accidental
7	53/M	Illicit drug and alcohol abuse	Pulmonary edema, brain edema, injection marks, no trauma, foam in lungs	Positive for cocaine, benzoyl-ecgonine, opioids, high cocaine and morphine concentration	Acute cocaine intoxication with recent morphine intake	Accidental
8	25/M	Occasional heroin, anxiolytics use	Vomit on pillow, lung foam and edema, injection marks, no trauma	Positive for opioids (codeine, morphine), benzodiazepines, THC, blood alcohol (0.44 g/L), opioids detected in hair	Respiratory failure due to opioid intoxication and benzodiazepine co-assumption	Accidental

DISCUSSION

Forensic PKs is an integral part of medical and pharmaceutical jurisprudence. The conducted research represents the overview forensic PKs. As mentioned earlier that term mainly deals with ADME of drugs in legal contexts and aids in determining drug intake timing and quantity that is primarily crucial in civil and criminal examinations. The study summarizes the relevance of forensic PKs by analyzing different recent research studies and stating the facts by employing and integrating the data from clinical forensic studies, toxicological reports, crime reports, and pharmacogenomics.[2, 5, 6, 8]

The review emphasizes the significance of understanding PKs in forensic sciences and investigations, particularly in cases where, narcotics or toxic material are involved. The study also highlighted the use of advance investigation tools, genetic variability and techniques to aid criminal investigations which may help in justice and public health concerns. Synthetic cannabinoid intoxication, such as MAM-2201 and AM-694, can be confirmed through blood and urine samples, allowing for long-term monitoring and short-term detection. These substances are found in plasma, urine, and hair, with their slower clearance rate making them suitable for short-term monitoring.[17, 24-26]

Opioid and cocaine-related deaths often involve a combination of substances, such as opioids, benzodiazepines, and alcohol, leading to respiratory failure, cardiac arrest, or brain edema. Case studies highlight the complexity of these drug interactions.[20, 21]Drug-facilitated sexual assault (DFSA) cases in France often involve benzodiazepines, opioids, and antihistamines, with accurate toxicological analysis crucial for identifying substances. Alcohol also plays a significant role in chemical vulnerability cases, with 90% prevalence in urine samples.[20, 21] Genetic polymorphisms in enzymes like CYP2B6 significantly impact drug metabolism, especially with drugs like antiretrovirals, antidepressants, opioids, and synthetic cannabinoids. Inter-individual variability in drug kinetics, influenced by factors like age, gender, ethnicity, and liver function, can affect forensic interpretations.[20, 21]

Post-mortem drug detection and timeline estimation are crucial in forensic cases. CYP enzymes' degraded enzyme activities provide a snapshot of pre-death metabolism, aiding in determining cause of death. Pharmacokinetic modeling and biological matrix data help estimate intoxication timelines.[17, 24-26]

CYP2B6 variants lead to altered drug metabolism, with effects seen in different populations (e.g., African and Asian populations show distinct drug response and ADR profiles) similarly genetic testing can clarify cause of death in drug-related fatalities, especially for individuals with poor metabolism or rapid metabolizers; the enzyme activities decrease rapidly post-mortem, with variability based on individual conditions and storage; Liver tissue at 4°C showed better protein stability than at 21°C; confounding factors (diet, exercise, other drugs) affect metabolic profiles, no single marker reliable for drug consumption due to variability across individuals; SNPs (Single Nucleotide Polymorphism) in CYP2B6 affect metabolism and adverse drug reactions, particularly in individuals with reduced liver function.[14, 37-39]

CONCLUSION

Forensic PKs plays imperative role in determining intoxication timelines, identifying death causes and linking substance use to criminal behavior. Factors influence forensic PKs investigations included: genetic variability, inter-individual variability, knowledge of ADME, drug interaction, intoxication timelines, post-mortem methodology.

RECOMMENDATIONS

The PKs of drug should be promoted more and utilization of advance tools in forensic sciences should be involved in employing better investigations to serve proficient justice in investigations of different crimes. Implementation of forensic PKs for generation of legal evidence against the accused person should be supporting legal document in criminal investigations.

DECLARATIONS

Competing Interests

All authors declare that they have no competing interests.

Funding
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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