

Evolving Need of Forensic Pharmacovigilance in This Era?

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Abstract

“Dying from a disease may be inevitable but dying from a medicine is unacceptable”. Patient safety is a prime concern for a medical professional. Pharmacovigilance Programme ensures the safety of patients by examining the pattern of adverse events that occur by the usage of drugs. In the current scenario drug abuse, misuse, adulteration, counterfeiting of drugs are exponentially increasing leading to numerous criminal, civil and suicidal cases in India. To investigate such cases and find out the root cause, forensic pharmacovigilance has been evolved and incorporated into our constitutional structure of India. Forensic pharmacovigilance experts must be having the knowledge and ability to understand adverse drug effects and other drug-related problems, legal questions and to detect criminal acts. Their skills and expertise are used in solving a diverse number of legal matters of drugs as misuse/ abuse/non-approved cases. which needs the medical Fraternity to come forward and work for the pivotal application of pharmacovigilance in the forensic sciences. In this review article, some drug reaction cases are discussed briefly that require legal implication for investigation

Key Words

Forensic Science, Adverse drug reaction, Pharmacovigilance

1. Introduction

Forensic science is a fusion of two Latin terms “forensic” and “science”. The word forensic relates to the application of scientific methods for the investigation of criminal cases that require a strong judicial implication and the word “science” defines a precise way of acquiring knowledge (Pickrell,2006). Collectively Forensic science is the utilization of technical methods and channel of investigation as it includes the activity to gather, protect and investigate the scientific evidence by code of conduct (Singh & Rastogi, 2017). Pharmacovigilance (PV) is defined as "the science and activities relating to the detection, evaluation, understanding, and prevention of adverse effects or any other drug-related problems"(Body et al, 2011). The

combination of these two critical components of medical sciences gives rise to a novel direction known as –Forensic Pharmacovigilance. (Sewal, Saini &Medhi, 2011)

Forensic Pharmacovigilance is constantly used by the experts in Pharmacovigilance providing their in-depth opinion during legal trials necessitates ADR's. In this write up we review the cases that required legal implications with the use of medicinal products. It may be due to the use of some counterfeit or substandard drug, drug abuse, drug overdose, misuse of over the counter (OTC) medication like pain killers or cough syrup, Medication error, etc. (Labadie, 2012)

The center of attention in Forensic Pharmacovigilance is knowledge of action to perform and interact with different reactions in chemicals in human beings and its implementation to legal matters. It is used in the detection of crimes that occur due to counterfeiting, substandard, overdose, or misuse of medicinal products. (Labadie, 2012)

2. Glossary

21 Adverse Drug reaction (ADR)

A Drug reaction that is noxious and unintended and that occurs at doses normally used in humans for prevention, diagnosis, or treatment of disease. It excludes therapeutic failures, overdose, misuse, noncompliance, and medication errors (Drug Induced death, Maryland, 2012)

ADR monitoring is a key component of Pharmacovigilance as well as crucial for the solution of medico-legal cases. (Sewal, Saini &Medhi, 2011)

22 Adverse Event (AE)

Any untoward medical event that may occur during the treatment with a pharmaceutical product but which does not associate with this treatment.[7]

When the relationship between an AE and a Drug is established it becomes an ADR.

23 Medico-Legal Case

A medico-legal case is one where, along with the medical treatment due to any illness or injury of a patient, also requires investigations by law, and it is significantly important to find out the reason for the current situation of the patient. (Sewal, Saini &Medhi, 2011)

Any case is required to be reported and registered as medico-legal where the patient needs OPD treatment.(Medical guidelines for patient care,2009)

24 Generic medicine

A generic drug having the same active pharmaceutical ingredients, strength, route of administration as the original drug; but excipients may differ. Generic products are sold only after the patent for the original drug is expires.[Generic drug, 2020]

25 Over the counter (OTC)

A medicine that is available for sale without any prescription.(Drug Induced death, Maryland, 2012)

26 Serious:

An untoward reaction that occurs at any dose, results in death or a life-threatening condition like requires to prolong hospitalization, significant disability, or congenital abnormality. (Drug Induced death, Maryland, 2012)

27 Counterfeit or substandard medication

A counterfeit drug is a pharmaceutical product that is manufactured by using inaccurate quantities of active ingredients, may contain ingredients that are not on the label, or maybe supplied with inaccurate or fake packaging and labeling. (Glossary of terms in Pharmacovigilance,2011)

28 Substance abuse

A person is substance abuse if consume the drug in a dose that is harmful and not within prescribed limits. That person may also get involved in various criminal or anti-social activities under the influence of drug(Singh &Rastogi, 2017)

29 Illicit Drug

Illicit drugs are substances that produce hallucinogenic effects that can either stimulate or inhibit the central nervous system. eg sedative and hypnotics.(WHO. Substandard and counterfeit medicines, 2004)

3. Why Forensic Pharmacovigilance?

Forensic Pharmacovigilance is vital to investigate drug cases related to forensic concerns. The main concept behind this is: Could the question drug (or chemical) produce the harmful effect? and did it cause the effect either 'beyond all reasonable doubt? (Singh &Rastogi, 2017)Forensic cases of the drug are rising day by day that requires deep investigation to find out the root cause and to achieve this, the specialization of forensic pharmacovigilance is necessary. The specialist of Forensic Pharmacovigilance must know about different drugs/chemicals and their interaction pattern in humans and their application to legal matters. The increasing incidence of criminal and civil cases creates the requirement to include forensic pharmacovigilance in the judicial system of India.(Labadie, 2012)

Several cases come in a routine with the use of counterfeit, misuse, overdose, abuse, spurious drug products or maybe occur due to local drug preparation without regulatory approval. Sometimes they may produce serious adverse effects and require legal proceedings.(Body et al, 2011) but the problem is that the data obtain from cases is not reliable in terms of completeness, biases, and quality This extensive evaluation is difficult for most clinical pharmacologists. Hence it is the need to develop a specialism within the existing area to sanction a separate segment of forensic pharmacovigilance.(Malve, 2016)

The Forensic Pharmacovigilance specialist must have the ability to analyze the blood samples, to analyze body fluids and tissue, and to interpret the data also having good knowledge of drug concentration (Minimum effective concentration and maximum tolerated dose of the drug), Toxicity range, or able to analyze the suspected case of poor adherence A pharmacologist is well-trained to detect any diversion in postmortem and antemortem blood levels and well knowledge various drug parameters as pharmacokinetics, pharmacodynamics, drug interactions, and adverse reactions.(Pickrell,2006)

A well-known example is the adverse drug reaction of bladder cancer that may occur with the prolonged use of pioglitazone, an antidiabetic drug. After this reaction reported the drug get banned in India It differs from Pharmacovigilance as it requires medico-legal implications. Hence Forensic Pharmacovigilance forms an interface between forensic medicine, toxicology, and pharmacology.(Mukherjee, 2007)

4. Case Studies of preceding Years That Require Legal Implications

There are a lot of cases due to drug overdose toxicity of sedative drugs, Pain Killers, Contaminated drugs, etc. in which death or other serious drug reaction occurs. Apart from the toxicological effects of drugs; certain adverse drug reactions require legal investigation of the case.(Sewal, Saini &Medhi, 2011).(fig 1). Various examples of drugs and their forensic significance which illustrates the relevance of drugs' knowledge in forensic concerns are enlisted below

Fig 1: Categorization of forensic cases relates to drug



41 Cases of forensic concern due to use of counterfeit or other substandard medicinal products

All developed and developing countries are affected by drug counterfeiting. Around 10% of counterfeit drugs are sold worldwide with higher prevalence in those areas where drug regulatory and enforcement systems are weakest. Any serious ADR caused by using counterfeiting or substandard drug case falls under the category of Forensic concern that requires investigation by law (El-Jardali et al, 2015): Cases of forensic concern due to using counterfeit or other substandard medicinal products are briefly discussed in Table 1

Table 1: Cases of forensic concern due to using counterfeit or other substandard medicinal products

S. No	Drug name	use/ Class of drug	Adverse drug reaction	Case briefing	comments	references
1	Sartans (valsartan, irbesartan, losartan)	Angiotensin II Inhibitor use to maintain blood Pressure	carcinogenic and genotoxic	Contaminated ingredients are used in large amounts to produce generic versions of an entire class of angiotensin II inhibitor blood pressure medications (collectively called "sartans") and after receiving drugs from this class, patients were exposed to genotoxic and carcinogenic effects. Findings revealed that to make the drug cheaper a chemical intermediate, tetrazole was changed during the manufacturing process and contaminated with N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA), which cause genetic damage and cancer.	The safety and risk associated with a chemically synthetic process should be thoroughly evaluated and understood.	(lowe, 2019), (Charoo, 2019), (Snodin & Elder, 2019)
2	Methylprednisolone acetate	steroid/ used in epidural steroid injection	Fungal meningitis	The first case of fungal meningitis was confirmed in Tennessee due to the use of epidural steroid injections which were contaminated by preservative-free methylprednisolone acetate. Epidural steroid injections were prescribed with voriconazole therapy and around 23 states had got this contaminated lots. The case count due to this is	Fungal meningitis pathogens that have been found in the investigation include <i>Exserohilum</i> and <i>Aspergillus</i> .	(Abbas et al, 2016) (Multi state fungal meningitis)

				around 751 patients including 64 deaths.	Species	gitis outbreak, 2012)
3	Paracetamol and diphenhydramine hydrochloride teething syrup	Analgesic and Antipyretic	Acute renal failure	In 2008 Ingesting teething syrup contaminated with diethyl glycol developed acute kidney injury (AKI) in several Nigerian children. A Total 109 case of Acute kidney injury was reported, among them, 87 patients died.	Good manufacturing practices should be used by all pharmaceutical manufacturer to Prevent such tragedy	(O'Brien et al, 1998) (Akus et al., 20
4	Heparin	Anticoagulant / use in hemodialysis	Allergic reactions as nausea, vomiting, diarrhea, low blood pressure, shortness of breath, redness or paleness of skin, sweating, headache, feeling restless, watery eyes, throat swelling,	IV bolus injection of Heparin was given to patients of renal dialysis and within few minutes, serious allergic reactions were developed as Heparin was counterfeit with oversulfated chondroitin sulfate (OSCS) in heparin active pharmaceutical ingredients (API) and finished heparin drug products. A total of 785 adverse reaction reports including 81 deaths were associated with this contamination	Rigorous Post-marketing surveillance at the national level is necessary to identify adverse reactions and to get control over possible counterfeit or drug adulteration.	(Labadie, 2012)

			thirst.			
5	Diphenhydramine	cough syrup	Acute renal failure and severe neurological dysfunction	Glycerine was contaminated by diethyl glycol (DEG) in preparation of cough syrup and this contamination results in a large outbreak including 105 deaths that occurred in the United States of America.	To make the formulation cheaper, diethylene glycol is used as it is less-expensive than glycerin for industrial applications; however diethylene glycol is nephrotoxic and can cause multiple organ dysfunction especially in children.	(Rentz et al, 2008)
6	Acetaminophen	NSAID/ Pain killer	Death	In 1982, Tylenol was widely used as a pain killer over the counter. Seven deaths have occurred after Tylenol consumption and investigations revealed that the Tylenol drug having 10,000 times the lethal dose of potassium cyanide.	It is an act of domestic terrorism in the United States that needs legal investigation.	(The tylenol murders, 2017)
7	Isonicotinic Acid hydrazide	Antituberculosis agent	precocious puberty	Seven children of age one to nine were given the drug INH as Anti TB medication from a single manufacturer lot and was developed Precocious puberty. Investigations found that the Drug INH was heavily contaminated with artificial estrogen that is diethylstilbestrol	Improved control on the manufacture of drugs is needed	(Weber, 1963)

42 Forensic cases due to pain killer

Pain killer is one of the major advancements of pharmacology as it gives relief from pain and inflammation but they may also develop serious adverse drug reactions and require legal investigation when consuming in high concentrations. (Joshi & Nadkar, 2005)] Table 2 enlist the cases of forensic concern due to pain killer (NSAID).

Table 2: Forensic cases due to pain killer

S.N O	Drug Name	Category	Reaction	Inference	Comments	Referen ce
1	Tramad ol	Opioid Analgesic/ used as pain killer	Death	The study revealed that a high concentration of Tramadol or overdose can lead to death and it is becoming a frequent cause of drug poisoning in recent years.	Tramadol overdoses cause respiratory depression and death	(Gioia, 2017)
2	NSAID	COX Inhibitor/ Used as Antipyretic, Analgesic	NSAID enteropathy	NSAID cause disease of the small Intestine. As they can inhibit both COX- 1 and COX-2 enzymes. This enzyme inhibition can interrupt the mucosal epithelium. And Subsequently increased permeability. Hence many irritants presenting the lumen of the bowel causes inflammation, erosion, and ulceration.	Death case is reported due to NSAID enteropathy. This is the case of potential hazards associated with NSAID abuse.	(Huddleston & Johnson, 2019)
3	Acetaminophen	NSAID/Pain killer	Toxic Myocarditis	Case of toxic Myocarditis occur due to Multidrug Overdose acetaminophen above therapeutic levels. Elevated serum alanine aminotransferase and aspartate Aminotransferase indicates the sign of hepatic injury. These findings clarified the toxic ingestion of acetaminophen	These type of diagnosis require a systematic investigation like autopsy as myocarditis is a rarer cause of sudden cardiac Death.	(Gosselin, 2017)

43 Forensic cases due to drug abuse or drug overdose

In 1969, WHO Committee on Drug dependence defined drug as a substance, which when consumed by a living organism, may alter one of its function. When a person is drug-addicted, he lost the power of self-control in respect of the drug which he is habituated. For example, alcohol and cannabis. Cases happened by Drug misuse or abuse are mainly Accidental. Besides, some cases also related to the synergistic effect of drugs to present fatal effects. However, homicidal uses of drugs have also been reported in stupefaction or forced illegal abortion cases.(Drug abuse; case studies, 2021)

Table 3:Forensic cases due to drug abuse or drug overdose

S.No	Drug	Category	Reaction	Inference	Comments	Referenc e
1	Tricyclic Antidepressants(TCA)	Psychotropic drugs	serious cardiotoxicity, respiratory depression, seizures, coma, and death	Studies revealed that Overdose of TCA or, sedative-hypnotics was a major method in suicide attempts.	Appropriate assessment of suicidality in psychiatry patients and careful monitoring of compliance may be needed	(Kim et al, 2015)
2	Potassium chloride	Potassium supplement	Heart attack	suicide attempt by intravenous injection of potassium leads to heart attack .	Suicide attempt by using potassium supplement is rare so the deep investigation is required to find out the root cause.	(Battefort, 2012)
3	caffeine	CNS stimulant of the methylxanthine class	GI disturbance including vomiting, abdominal pain and CNS symptoms like	Four cases of fatal intoxications with caffeine were found. Caffeine is readily available in beverages and different OTC products, with or	Over-the-counter selling of pure caffeine must be prohibited also It is suggested to include caffeine in the drug-	(Holmgran, 2012)

			seizures and supraventricular and ventricular tachyarrhythmias	without combinations with other drugs like ephedrine. Caffeine is believed to not much harmful but overdose of caffeine consumption either alone, intentional or not, might be deadly.	screening of forensic autopsy cases.	
4	Carfentanyl	A tranquilizing agent used in veterinary medicine (an ultra-potent synthetic opioid)	Death	Sixty-three death cases are reported from poisoning with the drug carfentanyl. The testing for the same was done by Forensic Medicine Service.	It becomes necessary to draw the attention of forensic medicine expert's towards new substance in the drug trade	(Fomin, 2018)
5	Diphenhydramine	H1 histamine receptor Antagonist	Cardiac Arrest and Death	Diphenhydramine is considered a safe medication but it shows dose- dependent toxicity. As high intake is correlated with death; therefore, caution should be taken in cases of a drug overdose.	Rapid measurement in the emergency department should be done on priority.	(Nishino, 2018)
6	Propofol	Short-acting intravenous General Anaesthetic	Respiratory depression and death	Abuse of the anesthetic agent propofol is rare, but an autopsy report of a 26-year-old male nurse Showed	Investigation revealed that death was not happened by a propofol overdose but due to respiratory	Iwersen-Bergmann, 2001)

				signs of toxicity and criminological evidence pointed towards propofol abuse and/or overdose.	depression that results from the overly rapid injection.	
7	Heroin	Opioid Analgesic	Death	The Maryland Department of Health and Mental Hygiene data for 2012 show that an increase in deaths related to a heroin overdose	In Maryland among younger age groups increase in fatal Heroin-related. The rise in overdoses from heroin is a new and concerning trend,	(Drug Induced death, Maryland, 2012)
8	Heroin and cocaine	Opioid Analgesic	Death	A 21-year-old woman was found dead as she is abuse by heroin and cocaine. Critical analysis was carried out by using liquid chromatography atmospheric pressure chemical ionization tandem mass spectrometry and the results revealed that combined action of an illicit drug overdose is the cause of her death	The investigation was done by using different methods to resolve the case.	Rojek, 2008)

5. Future Challenges

The medical profession is confidential to the public and it depends upon the subjective opinion of the professionals whereas law is open for the entire population and has a strong base of defined regulations. So both the areas need to work together for the success of the forensic pharmacovigilance program.(Singh &Rastogi, 2017) However, there are certain challenges while pharmacovigilance put forward its application in forensic sciences are:

- Globalization of increased drugs
- An exponential rise in the volume of drugs used
- Polypharmacy

All such challenges make pharmacovigilance complex and Under the light of these challenges, Pharmacovigilance now should be understood beyond only reporting the harms; rather it should be a rigorous risk-benefit assessment.

It is the responsibility of forensic pharmacologists to impart an accurate correlation between the drug concentration in the body and the associated postmortem report. Again the expert is free to give his/her opinion unbiasedly. Good pharmacovigilance practices (GVP) guidelines were introduced in 2012 by European Medicine Agency to set the standards of quality in pharmacovigilance. (Guideline GVP, 2012)It is vital to adhere to such guidelines while implementing pharmacovigilance in forensic areas. Hence It is pertinent to devise a code of conduct for such professionals to keep the benchmark of ethics in forensic sciences.(Sewel, Saini &Medhi, 2015) (Houck & Siegel, 2009)

6. Conclusion

As there is a continuous upsurging in medico-legal cases, expertise in drugs is required. Who resolve criminal and civil cases at various stages, understand pharmacokinetic and pharmacodynamics of drugs, etc. and able to validate between the uses of a drug with a specific associated outcome, The expert must be able to differentiate serious and non serious adverse drug reaction to establish a causal relationship between the drug and adverse event. and come up with data that will be helpful to the legal system to conclude and make the right decision .Hence to develop a discrete sub-discipline of forensic pharmacovigilance is necessary for the Medical education of India.

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