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The Spectrum of Toxicological Analysis in a Tertiary Care Setting-Pakistan

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ABSTRACT

Objective: To determine the frequency of opiate, cannabinoid, amphetamine, benzodiazepine, barbiturate, organophosphate, alcohol and related drugs of abuse poisonings in the tertiary care setting.

Study Design: Cross-sectional study.

Place and Duration of Study: Department of Toxicology & Therapeutic Drug Monitoring, Armed Forces Institute of Pathology, Rawalpindi, from Apr 2014 to Mar 2019.

Methodology: Random sampling was done, and specimens of blood in an EDTA bottle, urine in a plain container and gastric lavage in a syringe were collected for drugs of abuse (Opiate, Cannabinoid, Amphetamine, Benzodiazepine, Barbiturate, Organophosphate) and alcohol. The screening was done on fluorescence immunoassay and Microarray Technology, while confirmation was done on Liquid Chromatography-Mass Spectrometry/Mass Spectrometry (LC-MS/MS) for all drugs of abuse except alcohols and Gas Chromatography (GC-Head space) for alcohols.

Results: One hundred forty-six thousand six hundred one (146,601) toxicological tests were divided into two categories according to request forms; clinical toxicological cases 92,333 (63 %) and forensic toxicology 54,268 (37%). The maximum no of cases were routine toxicological analysis of blood, urine, and gastric lavage, 89,169 (60.8%) tests, and emergency toxicology cases were only 1,708 (1.2%) tests in clinical toxicology. Forensic toxicology included a maximum of no cases of routine workplace testing (two drug panel tests- cannabinoid and opiate) 43,850 (29.9%), and post mortem toxicology cases were only 6912 (4.7%). The frequency of benzodiazepine poisoning was maximum 1390 (28.5%) than cannabinoid and opiate poisoning, i.e., 180 (3.7%) and 210 (4.3%) respectively, in clinical toxicology cases. The frequency of benzodiazepine poisoning was still maximum 501 (22.2%) than Cannabinoid, Amphetamine and opiate poisoning, which were 1115 (12.6%), 190 (8.4%) and 380 (4.3%) respectively in forensic toxicology cases. Post mortem fluid toxicological analysis showed cannabinoid poisoning 82 (15.5%), opiate poisoning 20 (3.8%) and benzodiazepines poisoning 39 (7.3%).

Conclusion: Benzodiazepines, Cannabinoids, Amphetamine and opiate poisoning were extremely prevalent in Pakistan.

Keywords: Forensic toxicology, Liquid chromatography-mass spectrometry mass spectrometry (LC-MS/MS), Toxicology.

How to Cite This Article: *Fatima S, Hafeez A, Aamir M. The Spectrum of Toxicological Analysis in a Tertiary Care Setting-Pakistan. Pak Armed Forces Med J 2022; 72(4): 1172-1176. DOI: https://doi.org/10.51253/pafmj.v72i4.2918*

INTRODUCTION

According to different international guidelines and regulations; toxicology is divided into clinical toxicology (poisoning in emergency medicine) and forensic toxicology which is further divided into workplace drug testing (drug of abuse and alcohol), driving under the influence of alcohol and drugs and post mortem toxicology (medical and medico-legal) depending upon the clinical manifestation and purpose of testing for estimating the cause of death whether it was accidental, homicide or suicidal and whether the testing would be helpful in court of law.[1,2] International guidelines defined the toxicological established cutoffs for semi-quantitative detection in urine on fluorescence immunoassay or microarray technology i.e., screening methodologies and therapeutic and toxic cutoffs for different poisons in blood on liquid chromatography-mass spectrometry/mass spectrometry LCMSMS or Head space-Gas chromatography for confirmatory purposes.[3,4] Urine is considered, an ideal specimen due to its prolong detection period i.e., 3-4 days for opiate, benzodiazepines, amphetamine and cocaine. This detection period is up to 7 days in acute cannabis abusers and 28 days in chronic cannabis abusers. While detection period in the blood remains up to 24 hours for many drugs of abuse and 72 hours for cannabinoids. According to World Health Organization (WHO) data in 2012, 84% of death occurred in low and middle-class populations due to poisoning.[5] Worldwide, about 4 percent of the world's population aged 15–64 years were using cannabinoids in 2006 estimates and cannabinoid seizure in Pakistan was documented 18% in 2011, pesticides poisoning 15.3%, analgesics poisoning 8.7%, alcohol abuser 2.97%, opiate poisoning 5.38%, benzodiazepines poisoning

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Received: 20 May 2019; revision received: 25 May 2021; accepted: 15 Mar 2022

17.56% and methamphetamine poisoning 4.82% in male were observed.[6,7]

Toxicology is an unrecognized speciality in our country due to the lack of specialised trained staff in clinical toxicology. There are only two poison Centres in Pakistan, i.e., established by the International Programmed on Chemical Safety (IPCS) but without clinical toxicologists.[8,9] Toxicology branch has been less developed in Pakistan. Drug abuse and Alcohol consumption have emerged as significant social problems with a formidable economic impact in the modern era. Therefore, there is an increasing need for testing these parameters in various social settings, particularly in the Army setup. As a complete spectrum analysis of toxicology poisoning and sub-branches categorization for the generalized population was not done, we have planned a study whose objective was to determine the frequency of different drugs of abuse in the toxicology department at Armed Forced Institute of Pathology and to sub classify them into different classes of clinical and forensic toxicology.

METHODOLOGY

Ethical permission was obtained from the Research Ethics and Academic Division (READ) of Armed Forces Institute of Pathology, Rawalpindi (Cons/CHP-6/READ-1RB/19/405). A cross-sectional study was conducted to determine the frequency of different drugs of abuse from April 2014 to March 2019.

Inclusion Criteria: Individuals of both genders, aged 13 to 50 years were included.

Exclusion Criteria: Pregnant and lactating women, known habitual drug users and patients with co-morbidity like diabetes, hypertensive, chronic renal, heart and liver diseases were excluded from the study.

Random sampling was done, and specimens of blood in an EDTA bottle, urine in a plain container and gastric lavage in a syringe were collected for drugs of abuse (opiate, cannabinoid, amphetamine, benzodiazepine, barbiturate, organophosphate and alcohol. The screening was done on Alpha reader CHR 310, Triage which was based on the principle of fluorescence immunoassay and Microarray technology-Evidence Investigator.

In contrast, confirmation was done on Liquid Chromatography-Mass Spectrometry/Mass Spectrometry (LC-MS/MS) for all drugs of abuse except alcohols and Gas Chromatography (GC-Head space) for alcohols. Statistical Package for Social Sciences (SPSS) version 21.0 was used for the data analysis. Descriptive statistics for qualitative data were done with frequency and percentage, while quantitative variable Mean±SD. In inferential statistics, the test ANOVA (Post hoc test) was applied against different toxicology groups.

RESULTS

One hundred forty-six thousand six hundred one toxicological tests were done, which were divided into two categories according to request forms; clinical toxicological cases 92,333 (63%) (with history of intoxication), forensic toxicology 54,268 (37%), i.e., drug of abuse- workplace testing and forensic post mortem toxicology. The maximum number of cases was a routine toxicological analysis of blood, urine, and gastric lavage, 89,169 (60.8%) tests, and emergency toxicology cases were only 1,708 (1.2%) tests in clinical toxicology. Forensic toxicology included a maximum of no cases of routine workplace testing (02 drug panel tests-cannabinoid and opiate) 43,850 (29.9%), and postmortem toxicology cases were only 6912 (4.7%). The spectrum of clinical and forensic toxicological tests was shown in Figure.

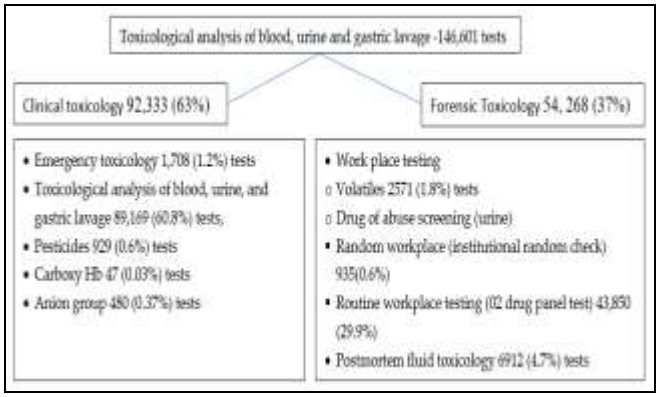

Figure: Study spectrum of clinical and forensic toxicological parameters showing distribution of total toxicological tests into clinical and forensic toxicology. Clinical toxicology tests were further divided into emergency, routine blood, urine and gastric lavage drug of abuse parameters along with pesticides, carboxy Hb, anion gap. Forensic toxicology tests were divided into workplace testing which include volatiles, urine drug of abuse (both institutional random check and routine) and postmortem fluid toxicology

Majority population 139,271 (95%) were male. The mean age was 26±05 years. The frequency of benzodiazepine poisoning was a maximum of 1390 (28.5%) than cannabinoid and opiate poisoning, which were 180 (3.7%) and 210 (4.3%) respectively in clinical toxicology cases. While other parameters; are barbiturate, amphetamine, methamphetamine, MDMA, Cocaine, Methadone, Buprenorphine, Phencyclidine,

Phenothiazines, Ibuprofen, Paraquat, Iron, and oxidizing agents were negative in clinical toxicology. The frequency of benzodiazepines poisoning was still maximum 501 (22.2%) than cannabinoid, amphetamine and opiate poisoning, which were 1115 (12.6%), 190 (8.4%) and 380 (4.3%) respectively in forensic toxicology cases, while no positive tests were obtained for Cocaine, Methadone, Buprenorphine, Phenothiazines, Ibuprofen, Paraquat, Iron, oxidizing agents. Postmortem fluid toxicological analysis showed cannabinoid poisoning 82 (15.5%), opiate poisoning 20 (3.8%) and benzodiazepines poisoning 39 (7.3%) and negative for the rest of all toxicological parameters as mentioned in the Table-I.

Table-I: Frequencies of Various Poisonings in Clinical, Forensic and Postmortem Fluids Toxicological Analysis (n=146,601)

Study parameters	Clinical Toxicology (Blood, urine and gastric lavage) Positive no. (Total Tests) Percentage Positivity	Forensic Toxicology (Urine-Drug of Abuse) Positive no. (Total Tests) Percentage Positivity	Postmortem fluid toxicology Positive no. (Total tests) Percentage Positivity
Opiate	210 (4879) (4.3%)	380 (8856) (4.3%)	20(531) (3.8%)
Cannabinoid	180 (4879) (3.7%)	1115 (8857) (12.6%)	82(531) (15.5%)
Amphetamine	(4879)	190 (2256) (8.4%)	0 (531)(0)
Benzodiazepine	1390 (4879) (28.5%)	501 (2256) (22.2%)	39(531) (7.3%)
Barbiturate	(4879)	22 (2256) (1%)	0 (531)(0)
Cocaine/Phencyclidine	(4879)	9 (2256) (0.4%)	0 (531)(0)
Tricyclic antidepressan	58 (4879) (1.2%)	8 (2256) (0.3%)	0 (531)(0)
Methadone	83 (4879) (1.7%)	(2256)	0 (531)(0)
Paracetamol	150 (7480) (2%)	0	(16)(531) (3%)
Salicylate	21 (5333) (0.4%)	0	0(9)(0)
Alcohol poisoning (Ethanol, methanol, iso-propanol, Acetone)	0	87 (2571) (3.7% Ethanol)	(4)(531)(0.7%Ethanol) (7)(531)(1.3% Methanol)
Pesticides	80 (929) (8.6%)	0	0 (531)(0)
Polydrug			
(Opiate and Cannabinoid) (Amphetamine & Alcohol)	0	283 (8856) (3.2%) 41 (2256) (1.8%)	0

ANOVA (post hoc tests) was applied to check the effect on three groups (clinical, forensic and postmortem toxicology), considering the age of patients as the dependent factor, which showed a non-significant correlation between groups and within groups against the age of patients as shown in the Table-II.

DISCUSSION

Our study was the first of its kind, which covers the whole spectrum of toxicological analysis, both clinical and forensic toxicology, due to its very large sample size. Our study showed that the rate of Benzodiazepine poisoning in both clinical (28.5%) and forensic toxicology categories (22.2%) was higher in our population than in cannabinoid and opiate poisoning. Benzodiazepine poisoning was also common due to the easy availability of sleeping pills and painkillers. As Benzodiazepines are combined with other drugs, their isolated use is very difficult to determine from various epidemiologic studies. Nevertheless, the existing data suggested that the lifetime prevalence of this drug in the United States was around 1% which increased to 2% in 2013.[10] Literature showed that from 1996 to 2013, benzodiazepine poisoning increased by 2.5% and 109% in 2003 and 2013.[11] In Pakistan, the epidemiological data on poisoning was very limited. A national survey in Pakistan showed that poisoning was the second most common cause of unintentional injuries. Pakistan has two poison information centres established by the International Programme on Chemical Safety (IPCS).[8] A study in 2016 in Pakistan showed that among poisoning cases, 87% were critical at the time of presentation, while psychiatric drugs were the cause of poisoning in 29% and alcohol and drug abuse was 2.97%.[7] Our population showed Cannabinoid poisoning was similar to another world. Very commonest drug of abuse in chronic abusers but less common in accidental cases as it was the most abused drug according to the 2014 World Drug Report. In Egypt, its poisoning was documented as about 2.7%–4.9% in the population of aged (15–64) years. Opiate poisoning was 3.4% equivalent in clinical and workplace forensic toxicology, possibly due to the intensive use of morphine derivative painkillers in an ICU.[12] There was an emerging phenomenon in opioid-dependent drug abusers in the United States of

Table-II: Post hoc tests showing effects of multiple comparison between clinical, forensic and postmortem toxicology (as independent variables) and age as dependent variables). Dependent Variable: age (n=146,601)

	(I) Groups	(J) Groups	Mean Difference (I-J)	SD. Error	*p*-value	95% Confidence Interval	
						Lower Bound	Upper Bound
Hydroxysteroid Dehydrogenase	Clinical toicology	Forensic toxicology-doa	6.40000	5.55627	0.489	-7.1508	19.9508
		Pm toxicology	0.93333	4.95373	0.981	-11.1479	13.0146
	Forensic toxicology-doa	Clinical toicology	-6.40000	5.55627	0.489	-19.9508	7.1508
		Pm toxicology	-5.46667	5.62705	0.599	-19.1901	8.2567
	Pm toxicology	Clinical toicology	-0.93333	4.95373	0.981	-13.0146	11.1479
		Forensic toxicology-doa	5.46667	5.62705	0.599	-8.2567	19.1901
Lysergic Acid Diethylamide	Clinical toicology	Forensic toxicology-doa	6.40000	5.55627	0.257	-4.8481	17.6481
		Pm toxicology	0.93333	4.95373	0.852	-9.0950	10.9616
	Forensic toxicology-doa	Clinical toicology	-6.40000	5.55627	0.257	-17.6481	4.8481
		Pm toxicology	-5.46667	5.62705	0.337	-16.8580	5.9247
	Pm toxicology	Clinical toicology	-.93333	4.95373	0.852	-10.9616	9.0950
		Forensic toxicology-doa	5.46667	5.62705	0.337	-5.9247	16.8580
Dunnett T3	Clinical toicology	Forensic toxicology-doa	6.40000	5.47788	0.575	-7.6304	20.4304
		Pm toxicology	0.93333	5.23913	0.997	-12.4836	14.3502
	Forensic toxicology-doa	Clinical toicology	-6.40000	5.47788	0.575	-20.4304	7.6304
		Pm toxicology	-5.46667	3.99237	0.449	-15.8233	4.8900
	Pm toxicology	Clinical toicology	-.93333	5.23913	0.997	-14.3502	12.4836
		Forensic toxicology-doa	5.46667	3.99237	0.449	-4.8900	15.8233

America: synthetic opioids were being replaced with heroin due to the increased availability of heroin in parts of the world and much lesser costs to regular abusers for developing their dependency. In 2014, in England, mostly opiate abusers were young similar to our study, and this poisoning accounts for 79% of the drug treatment population. Our study showed that Amphetamine poisoning was 8.4%, which was less in UK and USA. Opiate usage declined in the UK and was replaced by designer drugs like amphetamine, methamphetamine and cocaine, which were also expanding across South East Asia. Seizures of "ecstasy" increased by 2012 in East and South-East Asia, followed by Europe, which together accounted for 80% of global seizures of "ecstasy.[13,14,15] Our study showed much lower ethanol poisoning than the worldwide prevalence of ethanol poisoning, which may be due to the recreational nature of alcohol there and was not considered a drug of abuse by the World Anti-Doping Agency (WADA). Poly drug pheno-menon was also observed in our study but less than 5% among all total drug abuse cases, defined as the use of two or more substances at the same time or one after another.[16,17] Our study showed that the combined use of opiates and cannabinoids (3.2%) was most common than alcohol and amphetamine (1.8%). Mostly, poly drug was a common occurrence in recreational and regular or two drugs of abuse in different parts of the world.[18] Literature showed that there are two distinct patterns of polydrug use: One pattern is the use of different substances of abuse for complementary effects, for examples, Cannabis or Cocaine use with alcohol; other examples are the use of heroin with benzodiazepines or alcohol with other opioids (Methadone, Oxycodone, etc.) or cocaine with other stimulants.[19,20] Second pattern is the use of a drug to stop the side effects of another drug, e.g., cocaine and heroin use ("speedball").[21] We used two procedures for screening and two for confirmation on the state-of-the-art instruments, and these were the most frequently used methodologies for analysing drug abuse and alcohol.

Subcategorization of forensic sampling was not evaluated in previous studies.[22,23] Our study breakup down the sampling types based on clinical findings and the need for analysis which will be helpful for a better understanding of subtypes of forensic toxicology.[24,25] The postmortem toxicology poisoning spectrum was not analyzed previously, and our study results were indicative that cannabinoid poisoning was most prevalent in medico-legal autopsy and benzodiazepine poisoning was common in medical autopsy.

LIMITATION OF STUDY

We had not done postmortem tissue toxicology which also affects on results and prevalence of different poisoning in our nation.

CONCLUSION

Benzodiazepines, Cannabinoids, Amphetamine and Opiate poisoning were extremely prevalent in Pakistan.

Conflict of Interest: None.

Authors' Contribution

SF: Revision, data acquisition, manuscript writing, AH: Computation, MA: Revised manuscript.

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