Chapter

Forensic Toxicology

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Abstract

Forensic toxicology is a broad science that integrates principles and practices about toxicology and legal aspects, which occur in conjunction with medicolegal instances as with homicide, suicide, road traffic and other types of accident and/or disasters. Nowadays, the practitioners of forensic toxicology science have to deal with three chief sections, namely: postmortem, drug testing, and human performance forensic toxicology. Postmortem forensic toxicology is dealing mostly with investigation of abnormal deaths, or when drug intoxication incidence is assumed as a cause of death and no abnormal findings were detected during autopsy.

Keywords: forensic toxicology, postmortem, workplace testing, drugs of abuse, adulteration

1. Introduction

Toxicology; is the study of the toxic effect of chemicals or xenobiotic on living organisms, particularly the humans, or animals. Toxicology involves studying the symptoms, mechanisms, detection and treatments of poisoning of a living body. Chemicals, or toxic agents, may be biological, physical, or chemical. As the toxicology and science are in a continuous evolving status, the familiarity to the effects of toxic agents on human body keeps progression and advancement [1].

Toxicology is usually referred to as the "science of poisons," including the continuous study of all toxic effects of physical or chemicals compounds and the association between the causative defined dose and its effect on any exposed body [2].

Habitually, the toxicology is defined as the science representing the information, source, toxic or fatal effect, lethal dose determination, analysis of poisons and the curative methods used to treat any of such exposures [1].

2. Some definitions

A poison is a chemical or substance that can induce damage or death when our bodies are exposed to, and it is only the optimum doses that can distinguish a poison from a therapeutic agent. All known chemicals can lead to cellular damage or death under certain circumstances and if they exceeded permissible or therapeutic ranges. Therefore, a poison can be defined as any substance capable of producing injurious effects in a living organism.

Toxicologists are the trained experts who can evaluate the role of toxic substances and their adverse effects on living organisms or environment [2, 3].

The broad spectrum of probable toxic adverse effects and the endless lists of chemicals existing in our environment, together make toxicology a very broad field

of science. Consequently, many specialties of toxicology are needed to handle the numerous areas of toxicology science, including but not limited to; clinical, forensic, marine, and environmental toxicologists.

Forensics, by definition, is the use of science within the legal system to interpret a medical finding. The difference between clinical and forensic toxicology is not in the science or the methodologies used, but the difference lies in the end use of the attained results [4].

In clinical toxicology, the end user is a physician using the findings to treat and care for an intoxicated or poisoned patient, while in forensic toxicology, the end user can be a physician, a non-medical professional such as a lawyer, an employee, or police officer using the results to interpret a cause of death, employment eligibility, or compliance with workforce laws and terms. Hence, based on such situation the toxicologist may be a Physician, pharmacist, scientist, laboratory specialist or technician [3].

2.1 Main branches of toxicology

The professional activities of scientists and medical professionals within the field of toxicology fall into four main branches namely; forensic, industrial, clinical and environmental toxicology. Forensic toxicology is mainly concerned with the determination of the presence or absence and role of alcohol, drugs and their metabolites as well as other toxic substances in biological fluids, and/or tissues to solve a medico legal problem [5].

Based on that forensic toxicology is mainly referred to the science entailing the fusion of analytical forensic chemistry with toxicological principles and effects, dealing toxic substances, drugs of abuse, doping agents, chemical warfare agents, and their metabolisms and analyses, which are related to laws and ethics. Scientists responsible for testing bodily fluids and tissue samples during autopsies looking for the presence of chemicals, as well as laboratory specialists concerned with determination of presence or absence of any recreational drug or substance in samples collected from employees, or sportsmen are usually referred to as forensic toxicologists. Such toxicologists work mainly in laboratories to perform tests on samples collected by crime scene investigators, or workplace or sport officers [2–4].

Forensic toxicology laboratories handle the analytical procedures performed on both biological and sometimes non-biological samples to search for controlled substances. Following that, they generate analysis reports requested by the criminal justice system, or workforce departments. All Forensic Toxicology providers should exert sound efforts to guarantee that all their analytical results meet high ethical and moral standards and that all working personnel adhere to relevant legislation of the country [1].

The forensic toxicology laboratory should have standard operating procedures (SOPs) that are complete, updated, and accessible to all toxicologists carrying out forensic toxicology tests. SOPs should include detailed descriptions of all procedural processes starting from sample receiving, fulfillment of secured chain of custody, analysis, quality assurance and quality control (including validation of methods), reviewing of data, reporting and sample disposal as well as electronic program usage and security protocols of such programs if any. Their performance should be thoroughly and periodically assessed to accept the results released by their laboratories [3].

Forensic toxicology jobs most of the time involve testing for the presence of toxic gases (e.g., carbon monoxide, hydrogen sulfide, or phosphine); illegal or medicinal drugs; toxins; liquor; metals or elements; and other toxic substances when intoxication or drug poisoning are anticipated. Their scope of responsibility may include

analyzing samples from criminal cases, and once their analytical reports are ready, they might present their testimony about it in a court of law [4].

Using highly specialized tests, methodologies and state-of-the-art equipment, chemical and biomedical instrumentation and chemical reagents, forensic toxicologists are requested to determine either the presence or the absence of chemicals while documenting each step of the process, and to determine the concentration of any detected substance to help finding out whether or not such xenobiotic was a cause of an unexplained death, accident or act [5].

The majority of forensic toxicologists are employed by law enforcement agencies, private drug testing facilities, and governmental bodies as Ministry of health in some countries. In forensic toxicology the main interest is the extent to which drugs and poisons may have contributed to impairment or death. In the field of forensic toxicology, the accreditation is important. It requires a great deal of energy and expense but does not, however, warranty all of the quality levels needed.

The conformity of a forensic toxicology laboratory with acknowledged quality and management structures is currently mandated in many countries, to be able to accept their analytical results and reports. As there are an essentially unlimited number of poisons that may be present in individual cases, therefore forensic toxicology is a scientific discipline in which everlasting efforts should be constantly exerted to complete and improve the methods of poison detection and show its close relation to raising quality [4–6].

Forensic toxicology can hence be generally divided into three main sectors [2–4]:

- *Workplace or pre-employment testing* dealing with pre-employment drug screens or drug screens required by the workplace.

- *Postmortem toxicology* dealing with the toxicology testing on deceased individuals and is a routine part of the autopsy process. Main aim is establishing the cause of death and clarifying its circumstances in postmortem investigation. Postmortem toxicology involves not only determining the presence and the amount of toxic substance in the postmortem body, but how the body's natural processes affect the substance, including chemical change and dilution.

- *Human performance testing* or Criminal Toxicology is used to elucidate the absence or presence of substances modifying human performance or behavior. This could be dealing with the determinants or toxicological factors in the investigation of criminal offenses, driving under the influence of alcohol or drugs, committing a crime while on a drug, or having a crime committed against an individual such as a sexual assault.

Therefore, the work of forensic toxicologist is considered as highly complicated as small quantities of poisons and their metabolites are to be isolated, purified and quantified from a highly complex matrix. Individual Forensic Toxicology specimens should be handled in such a manner as to reduce the possibility of degradation, contamination, adulteration, and/or damage during all steps from collection to transport, analysis and finally result reporting. Conventional transportation of specimens to the toxicology laboratory might include manual delivery, postal shipments, or a private courier service. A chain-of-custody form should be designed that will accompany specimens from the place of collection to the laboratory [7].

3. Workplace drug testing

Workplace drug testing is divided into two divisions, regulated and nonregulated testing:

- Regulated testing is testing that is mandated by the government via the Ministry of Health Services. This testing is mostly mandatory mainly for drivers, all governmental employees, military employees, and for those with many other jobs, in most of the countries.

- Non-regulated workplace drug testing is any testing that is required of a new employee to start a job, or it might be requested by workplace as random unplanned frequent screening for some workplaces as for pilots, workers in sensitive positions, or soldiers. The guidelines are not as strict as regulated testing, although the basic tenants are still adhered to [1].

3.1 Samples used for screening in workplace testing

3.1.1 Urine sample

The specimen for regulated workplace testing is always urine, but in some countries, an additional sample is requested, which might be oral fluid sample, or blood sample. It must be collected under direct observation or with measures in place so that tampering with the collection are eliminated, as by using adulteration detection kits directly after sample collection by donor, where the samples proved to be adulterated are rejected before being received by the laboratory personnel.

Secured chain of custody is applied for all samples collected since their collection till the release of the final Analytical report [7].

3.1.2 Blood sample

Blood sample is of particularly useful to the forensic toxicologists since the drug or poison existence in blood shows that exposure followed by absorption has taken place, hence a recent exposure might be ascertained. Furthermore, significant associations exist between the blood levels of most chemicals, poisons or drugs and their pharmacological and/or behavioral effects exerted on living bodies. On the other hand, urine drug levels, only indicate a previous drug exposure without conclusive evidence about the exact time of possible exposure or its probable physiological effects [4].

3.1.3 Oral fluid sample

Oral fluid is getting recent credit as a standard matrix for rapid drugs or substances of abuse detection. When compared to blood and urine samples, the oral fluid collection is non-invasive, easy technique with negligible intrusion into personal privacy. Such a sample can be collected under direct observation, consequently excluding the likelihood of sample exchange or adulteration as seen with urine samples. Hence, oral fluid can be beneficial in numerous situations that necessitate drug testing, as workplace screening, drug monitoring follow up, or for definitive treatment [2–4].

When compared to urine samples, oral fluid is a better reflection of blood concentrations of a drug. It specifies recent drug use and offers better association with pharmacological effects such as impaired driving performance. Hence, recently it is considered as the most appropriate biological matrix that enables roadside testing in

road traffic accidents or other situations mandating the diagnosis of driving under the influence of drugs or alcohol.

It is becoming a more accepted testing specimen, due to the ease of its collection. Being an ideal specimen to collect where a restroom is not available, such as at the scene of a traffic accident, popularity of using oral fluid sample is increasing by time. As oral fluid is a hyper filtrate of blood, parent compounds are detected opposed to metabolites. Detection lengths are thus shorter than in urine, being only 1–2 days compared with 2–5 days with urine [7].

3.1.4 Hair samples

Hair is an alternative sample type that can be used for drug testing. The main advantage over the other samples is the wider length of detection, as in hair it might reach up to 3 months. However, environmental contamination is a major concern with hair testing, so laboratories must take special precautions during specimen preparations to ensure removal of environmental contamination.

3.1.5 Human breath testing

Lastly, another biological sample that has established recognition in many global areas in forensic toxicology testing is human breath. It is usually sampled for the detection and estimation of blood alcohol concentration in an individual and the detected level will be compared with the legal level of each country for driving under the effect of alcohol and other driving related offenses. It may also be sampled for the presence or absence of inhalants, most of which are volatile organic solvents that are not easily detected in blood, that are getting more abused among youths and adolescents [1–5].

3.2 Urine sample adulteration

Specific precautions are required to determine if the specimen has been tampered with or adulterated in any way. All urine samples should be tested for creatinine, specific gravity, pH, and oxidants (nitrites).

When specimen adulteration testing falls out of the specified ranges of what is considered normal, it is termed as one of four classes, namely; diluted, substituted, adulterated, or invalid.

3.2.1 Diluted sample

A substituted specimen will be identified if [2–7]:

- The serum creatinine level exceeded 5 mg/dL or was below 20 mg/dL; and
- A specific gravity above 1.0010 or below 1.0030.

3.2.2 Substituted sample

Substituted sample is generally applied to non-human samples submitted by the donor during testing process. Any sample will be reported as substituted one if:

- The serum creatinine level was below 2 mg/dL; and
- The specific gravity is less than or equal to 1.0010 or greater than or equal to 1.0200.

3.2.3 Adulterated sample

If the donor has added any substance to the collected sample, this will be referred to as an adulterated sample. Such sample should be reported as adulterated when any of the following criteria is encountered:

- pH < 3
- pH ≥ 11
- Nitrite ≥ 500 mg/mL
- Presence of chromium
- Presence of a bleach, iodine, or fluoride
- Presence of glutaraldehyde
- Presence of pyridine
- Detection of surfactant

3.2.4 Invalid sample

A specimen will be reported as invalid when any of the following conditions is met:

- Creatinine concentration and specific gravity results are discrepant: Creatinine < 2 mg/dL and specific gravity > 1.0010 or < 1.0200
- Creatinine is ≥ 2 mg/dL and specific gravity is ≤ 1.0010.
- pH is outside the acceptable range: pH ≥ 3 and < 4.5
- pH ≥ 9 and < 11
- Nitrite ≥ 200 mg/mL and < 500 mg/mL.
- Urine that falls into any of these four categories is considered to have failed the drug test, even if the tests for drugs are all negative.

4. Postmortem testing

Analytical toxicology is a main procedure following the autopsy process. In postmortem setting and directly after death, metabolism of drugs and chemicals cease. If an autopsy is performed within a reasonable time frame, and the body was protected from harsh environmental conditions, the toxicology results will be as close as possible to what was in the body directly at the time of death. Quantitation of any drugs can indicate if an overdose occurred, a sub-therapeutic drug level was present, or a combination of multiple substances contributed to the cause of death [8].

In contrast to workplace drug testing, where urine samples are usually analyzed for a relatively fewer drugs and/or drug metabolites, the scope of work in postmortem forensic toxicology often encompasses search analysis for a larger number of

poisons and drugs in numerous altered samples including blood, gastric contents, vitreous, and tissues including; renal, liver, spleen, muscle and brain tissues [5].

In addition, analysis of blood is mostly noteworthy as lethal drug concentrations in blood are well known for most of the drugs. However, drug concentrations in blood are generally lower than in urine or in tissues, which make their detection much harder than in urine samples [3, 5].

In many occasions, the forensic pathologist is dependent on the toxicological results to offer aid in determination of the cause of death. This is usually the situation when either gross or microscopic examinations during the autopsy process do not interpret a cause of death [9].

The forensic pathologists' requests of the forensic toxicologist have transformed over the last years. Before, they mainly requested identifying and reporting any lethal drug and/or poison levels that eventually lead to death. Definitely, due to the obvious limitations in the methods available at that time, this was the only possible request [10].

Accordingly, many drug-related deaths before were probably pass unobserved. But in modern times, larger scope of results and interpretations were requested from forensic toxicologists to clarify, including reporting drugs given at therapeutic or even sub therapeutic doses.

Such contribution might help to determine whether the deceased was compliant in taking the prescribed medicine. Many questions can be easily answered by toxicologists in current years as finding out whether noncompliance contributed to the death occurrence or not, or did the simultaneous use of many groups of medication together at therapeutic doses lead to unwanted drug interactions.

Another common question encountered by forensic pathologists is to clarify whether or not the deceased was under the effect of drugs at the time of the fatal accident, or was the suspect of the homicide under the influence of illegal drugs. Nowadays, such queries can best be easily answered by forensic toxicology laboratories equipped with state-of-the-art chromatographic instruments attached to mass spectroscopic units [1–3, 5].

4.1 Specimen

Postmortem testing is not limited to only urine. Specimens can be blood, urine, vitreous humor, gastric contents, liver tissue, hair, fingernails, or bile. This is not a comprehensive list. In postmortem investigations, the types of samples and tissue specimens and fluids needed for toxicological investigation are based often on the body condition and the type and/or number of analytes that must be identified and hence quantified. The toxicologist should also be informed about any putrefactive state of the body, injuries owing to the manner of death and other autopsy findings [3].

Many deaths involve ingestion of multiple drugs, necessitating larger amounts of tissue and fluids to be collected at post-mortem examination for toxicological examination. Prior to tissue extraction and analysis, all analyzed tissues must be homogenized. Water or buffer solutions such as sodium phosphate, might be added to the tissue sample preceding homogenization. It is vital to record the tissue weight as well as the fluid volume used to homogenize tissues in, as such data is of utmost importance in correctly estimate the drug concentration per each tissue weight unit [10].

Effective sample extraction and non-contamination are additional analytical process challenges while dealing with postmortem samples collected from decomposed bodies. Decomposition Products, can diminish the efficacy of extraction and produce interfering peaks during the analytical processes using chromatography methods. Also, tissue homogenates containing fatty materials must be separated from the drug analytes prior to analysis [1–3].

Basic drugs can be efficiently separated from lipid material by a process known as back-extraction, where the extracted drug from the tissue homogenate into a water-immiscible organic solvent and then back-extracted into a dilute acid solution where the neutral lipid material remains in the immiscible organic solvent, and the dilute acid solution will be turned basic to re-extracted the drug again into an organic solvent [1–3, 5].

All items collected from the death scene such as powders, pills, syringes, tools or liquids must be sent for analysis as well. A precise report including full description of the sample type and the site of collection should be prepared and sent to the laboratory with the samples needed to be analyzed. Blood samples can be collected from different body parts, as each area or collection compartment can have a varying drug concentration. Central blood samples can be collected from the heart, jugular, subclavian, and femoral veins, while blood collected from other sites is called peripheral compartment blood [2].

Preferably, blood samples must be collected from central and at least one peripheral site, to overcome the probability that any of these sites might be contaminated owing to different death manners. Blood is usually collected into preservative treated tubes, to stop further blood sample decomposition. Another important factor is that most of collected specimens are often stored for extended time periods. Samples' states might be deteriorated by bacteria, which might give erroneous results' interpretation mainly for ethanol levels. Based on putrefactive state and manner of death, certain specimens may become contaminated with bacteria, either via exposure to the normal flora or through external contamination, as in case of a body with multiple open wounds or gunshots. The collection of specimens as well as the testing of these samples should always be performed under chain of custody. Postmortem blood is difficult to work with as a result of coagulation and/or degradation, and because of the state of the specimen at the time of testing [11].

4.2 Specimen type, amount and site of collection

The following is a suggested list of specimens and amounts to be collected at post-mortem in such cases [3–6, 9]:

- Femoral blood: at least 10 mL (site specified and suitably isolated).
- Urine: all available sample.
- Vitreous humor: all collected sample.
- Cavity/heart blood: not less than 25 mL, collected only if femoral blood is limited or not available.
- Hair: to be collected at the start of the autopsy prior to body evisceration.
- Bile sample: 10 mL.
- Liver, renal and/or spleen tissues: 10–20 g, mainly if low volume of blood available.
- Stomach contents: all available and any examples of undigested tablets/drug material (including potential plant toxin material.
- Brain tissue: 10–20 g (for volatiles).
- Lung tissue: 10–20 g (for volatiles).

- Samples collected by in health care facilities prior to death (ante mortem specimens) are samples of greater importance.

- Non-human items collected at the from death scene, which may have contributed to the death are considered as samples of utmost importance, in toxicological investigation in postmortem cases.

5. Human performance testing

How an individual acts when under the effect of a substance or drug of abuse is determined by human performance testing. This type of testing includes determination of blood alcohol level and drugs of abuse testing from a suspected driver. Blood testing for drugs from a potential drug assisted sexual assault, or testing of a worker exhibiting weird behavior while at work is another aspect of human performance testing. Criminal Toxicology is another aspect of human performance testing, where the determining factors or toxicological causes during the investigation of any criminal offenses have to be studied [12].

5.1 Specimen

The specimen of choice in human performance testing is blood, though oral fluid sample is another promising sample. Analyzing a blood sample is of utmost importance because upon confirming the presence of any abused substance, it is then probable to establish an estimated time frame of drug or substance exposure. Such finding is not likely to be estimated upon using a urine sample, where all drugs have a much longer detection window. Ability to conclusively verify the timeframe of drug consumption, is crucial in all human performance testing settings [3].

6. Types of testing in the field of forensic toxicology

6.1 Screening or initial testing

Initial testing of collected specimens, is known as screening or screen testing. It is done by immunoassay methods. The cutoffs to determine negative from nonnegative samples are established by Governmental regulatory bodies in each country. Any value greater than or equal to the cutoff is considered "nonnegative" (The term positive can only be used with confirmatory testing because of the possibility of false-positive screening test). Screening testing is done for a specific class of drugs; opiates, amphetamines, benzodiazepines, etc.

If all performed initial screening tests were negative, the results will be released as negative and there is no further testing to be requested. If any of the performed test results were equal to or above the cutoff value, a new aliquot from the main sample will be obtained and confirmatory testing will be started.

The initial identification or detection of drugs and other toxins by an immunoassay or enzymatic screening methods should be confirmed by a second procedure utilizing a different analytical principle. It is to be well stated that the use of a second immunoassay screening system (e.g. RIA—radioimmunoassay) to confirm another immunoassay result (e.g. FPIA—fluorescence polarization immunoassay), is not acceptable, even if it is supposed to be a more specific assay or testing procedure. Final results are not released until all confirmatory results are finalized [13].

6.2 Confirmatory testing

The forensic toxicologist is usually confronted with the hard mission of screening a given sample for the "unknown". The toxicology laboratory consequently must be equipped with state-of-the-art instruments, capable enough to perform a wide range of toxicological tests with high specificity. This procedure is usually referred to as "systematic toxicological analysis" (STA), or "general unknown screening".

All chemical substances exposed to screening procedures, must be firstly separated from the liquidified biological matrix. The simplest sample preparation method is to use a water miscible solvent, as acetonitrile or acetone. Such solvents will be added to the biological fluid to precipitate protein and other unwanted constituents. A filtration or centrifugation step follows before the extraction processes that end up with a more concentrated extract than the original sample, followed by the final confirmatory analytical step.

Confirmation testing is performed by detector as mass spectrometry, coupled either to Chromatography technique that provides a chemical separation of analytes in a gaseous (GC) or liquid (LC) system namely; gas chromatography or liquid chromatography. The selected detector should be appropriate to the analytes among other factors. The testing occurs on a fresh aliquot from the original sample, to exclude likelihood of a possible erroneously mix up with the initial screening aliquot [11].

For each drug class to be screened, there is a group of specific confirmatory tests. Such analytical confirmatory testing result is conclusive, and indisputable, when the testing process is performed correctly. Such an assurance is partly based on the fact that the confirmed result was reached based on multiple parameters, e.g.; retention times, parent and daughter ions ratios. If confirmatory testing procedure is performed correctly and properly maintained through applying proficiency testing with similar laboratories, the confirmation test is considered to be definitive and undisputable [9].

7. Result reporting

Reporting of the results is done following a second review of all results by another laboratory personnel who was not a part of the testing process. On finding them acceptable, all results will be certified and released either to the medical review officer or to the requesting entity [1–3].

A medical review officer is usually a physician acting as an intermediary between the Toxicology laboratory and the requestor or client who ordered for the test. The medical review officer should be well trained to communicate with the client, donor, and legal representative and/or forensic pathologist to help interpreting the testing results. They are responsible to deal with a donor whose samples proved to be positive, and determine if the detected drug was taken complying with a physician's instructions or were recreationally abused [5–7].

Following the release of a final report, it might turn out to be essential to correct an error that might be typographical or otherwise. A corrected report should be issued in this occasion comprising the same demographic data as in the original report(s) and be well labeled as a corrected report replacing the original faulty one.

Forwarding samples to another laboratory for analysis or result evaluation, should be well recorded and referred to on the final report/statement demonstrating this fact. Results of referred laboratory tests may be integrated into the original laboratory's final report/statement, but the name of the laboratory that truly carried out the test should be clearly stated [1–4].

8. Accreditation

Forensic toxicology laboratory accreditation is an important recommendation to standardize the results. Proficiency testing and comparing results to certified regional laboratories is an initial step during the journey to laboratory accreditation [3, 5–8].

Conflict of interest

No conflict or competing of interests to declare.

Thanks

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Acronyms and abbreviations

GC	gas chromatography
FPIA	fluorescence polarization immunoassay
LC	liquid chromatography
RIA	radioimmunoassay
SOPs	standard operating procedures
STA	systematic toxicological analysis

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