Chapter

Introductory Chapter: Medical Toxicology

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1. Introduction

Toxicology is "the study of the occurrence, properties, detection, adverse effects, and regulation of biological, chemical or physical agents on living organisms." Modern toxicology focuses on the adverse effects of toxic substances (including toxins, venoms, and toxicants) at molecular level [1, 2].

Since toxicology is a multidisciplinary science, the contributions and activities of toxicologists are widespread and diverse. Toxicologists are mainly concerned with the mechanisms of action of different agents as, we now know, all agents can lead to toxicity due to the exposure period and dose. However, for even the most known and oldest agents, the pathways or endogenous molecules they affect to create toxicity are still being investigated by scientists. As toxicologists, we also contribute to other scientific areas including medicine, physiology, and pharmacology while we receive the help from several branches of science. Toxicologists mainly recognize, identify, and quantify the hazards of foods, pharmaceuticals, workplace chemicals, household products, cosmetics, and personal care products along with toxins and venoms. Furthermore, toxicologists who work as members of academic, industrial, and governmental organizations can also develop the standards and regulations in order to protect human and animal health as well as the environment from the adverse effects of microorganisms, chemicals, or physical agents. In the modern era, toxicologists share methodologies and scientific knowledge to obtain accurate data about the unwanted effects of different agents [1, 3, 4].

2. Poison, toxin, toxicant, and venom

Poison is any substance that leads to harmful effect/s to a living organism when taken by any route, either by accident or design. The history of poisons and poisoners has a long record dating back to the ancient times. In Homer's *Odyssey*, the first use of a specific antidote was documented. In three books (*De Antidotis I*, *De Antidotis II*, and *De Theriaca ad Pisonem*) written by Galen (AD 129–200), the development of a universal antidote was described in detail. Later, Nicander (197–170 BC) focused on the prevention of the gastrointestinal absorption of poisons, emesis induction by using an emetic agent and the mechanical stimulation of the hypopharynx. Greeks and Romans used oral wood charcoal to treat diseases such as anthrax and epilepsy. After 1960s, the use of activated charcoal was routinely recommended in many poisonings [5].

Paracelsus (1493–1541), the "Father of Toxicology," was a physician-alchemist. He formulated many revolutionary ideas that form the basic structure of toxicology, pharmacology, and medicine today. The scientist indicated "*Dosis facit venenum*," which simply means "All substances are poisons; there is none which is not a poison.

It is the dose that differentiates between a poison and a medicine." Therefore, poisoning is a quantitative concept, and we now know that the right dose distinguishes "a poison" from "a remedy." It can be stated that "Almost any substance, including water, can lead to toxicity at high doses without causing any harmful effects at lower doses." However, we also know that some chemicals can also lead to toxicity at lower doses and the harmful effect will not significantly increase at higher doses. The toxicity of some endocrine disruptors, particularly bisphenol A (BPA), is an example [1].

There is a certain difference between "a toxicant" and "a toxin" and they are not used as synonyms. Many people do not clearly know the difference and instead they refer every harmful substance as "a toxin." Toxicants are synthetic, human-made, and toxic chemicals which are capable of causing deleterious effects on living organisms. Toxicants are significantly different from toxins not only because of their synthetic origins but also because of their production volumes and masses, distribution processes, and structural heterogeneity. They can be present in houses, workplaces, living organisms, and environment. On the other hand, toxins are small molecules, peptides, or proteins that are produced by living organisms. In general, toxins are metabolic products, which are parts of the defense mechanisms of animals, plants, insects, microbes, etc. against other living forms. The term "biotoxin" is occasionally used to explicitly confirm the biological origin. The organisms produce them in order to predate or repel (such as in the snake, scorpion, spider, jellyfish, and wasp toxins) or defense (honeybee, bee, ant, wasp, termite, and dart frog toxins) [6, 7].

The action of toxins has long been recognized and understood throughout human history. Toxins from plants are associated with murder, assassination, and suicide. The deaths of several famous historical figures have directly or indirectly involved toxins from poisonous plants. Socrates was forced suicide with a toxic alkaloid from poison hemlock (*Conium maculatum*), while the many victims of Livia (wife of Emperor Augustus) and Agrippina (wife of Claudius) succumbed to the toxic tropane alkaloids of the deadly nightshade (*Atropa belladonna*) [7–9].

A common characteristic of natural toxins is to cause deleterious effects with small quantities on the metabolic and physiologic functions of a living organism. Toxins usually interact with biological macromolecules like enzymes or with cellular receptors. Toxins vary greatly in structure. Moreover, their harmful effects can range from minor (such as a bee sting) to almost immediately deadly (such as botulinum toxin). A systemic toxin affects the entire body or many organs rather than a specific site. An organ toxin affects only specific tissues or organs [10].

A "venom" is a secretion of an animal (like snake, spider, and scorpion) that contains one or more toxins. Venoms usually are classified into four major groups according to their mechanisms of action: (i) *Necrotoxins*, which cause necrosis in the cells they encounter (e.g., viper venoms), (ii) *Neurotoxins*, which primarily act on the nervous system of the exposed living organisms (e.g., box jellyfish, scorpion, octopus, cone snail, centipede, and black widow spider venoms), (iii) *Cytotoxins*, which kill the exposed individual cells (e.g., black widow spider venoms), and (iv) *Myotoxins*, which damage muscle cells by binding to a receptor (e.g., snake and lizard venoms). Due to the highly specific and potent effects of venoms, they often serve as excellent candidates from which therapeutic drugs may be developed. As venom peptides and proteins affect the mammalian physiological processes, these structures can assist in creating targeted libraries of potential drug candidates. They are extremely site-specific in their actions and this specificity can provide a value as a lead therapeutic or biological probe [11, 12].

3. Medical toxicology

Medical toxicology is a subbranch of toxicology, which is concerned with providing the diagnosis, management, and prevention of poisoning and other adverse effects of drugs, cosmetics, personal care products, occupational and environmental toxicants, and biological agents. Medical toxicology mainly deals with the prognostic indicators of poisoning severity and predictors for the treatment. For practical reasons, much of this work has been retrospective in nature; however, it has resulted in significant aids to guide the treatment rendered by clinical toxicologists. Medical toxicologists are involved in the assessment and treatment of a wide variety of problems, including acute or chronic poisoning, substance abuse, adverse drug reactions (ADRs), drug overdoses, envenomations, industrial accidents, and other chemical exposures. Generally, physicians who are specialized in emergency medicine, poison management, and pediatrics can become medical toxicologists. Medical toxicologists work on finding new and effective antidotes and treatments in order to prevent poisonings and xenobiotic injuries. Medical toxicology is closely related to clinical toxicology, with the latter discipline encompassing nonphysicians (generally pharmacists) as well [13–16].

Poisoning is a significant global public health problem. Childhood poisonings were recognized as a significant component of pediatric practice and patient morbidity in the 1930. However, little information was present on the toxicity of household products and management recommendations at that time. A Duke University pediatrician, Jay Arena, tried to systematically collect, analyze, and distribute the clinical information to physicians about childhood poisonings. In a case series, the researcher described the clinical outcome of 50 lye-poisoning cases. This was one of the first reports on the hazards of household products to children [17].

Medical toxicology has been improved by the evolution of poison control centers. Poison control centers were established to provide drug and chemical toxicity information and patient management guidance to physicians. These services were expanded to handle telephone calls from laypersons in the 1960s. Arising out of a growing concern over the rising incidence of poisoning worldwide, coupled with a lack of public awareness about its seriousness, poison control centers mainly serve for the public in order to direct information to patients and health-care professionals today. A poison control center is usually managed by a medical toxicologist who specializes in poisonings. These centers also recruit educators for poison prevention programs and provide education activities for health-care personnel and poison prevention organizations [18–20].

In 2017, 84% of poison exposures reported to US poison centers were nontoxic, minimally toxic, or had at most a minor effect. Intentional exposures were significantly more serious, with a 30-fold greater percentage of serious outcomes (major or fatal effects) compared to unintentional exposures. Exposures in teens and adults were also considerably more serious, with 19.09% of teens and 17.91% of adults having a moderate, major, or fatal effect compared to 1.10% of children younger than 6 years. In 2018, 12.1% of poisonings in the USA arose from cosmetics/personal care products, while cleaning substances (household) and analgesics caused 10.7% and 9.0% of the poisonings, respectively. In the same year, analgesics were responsible for 10.9% of all drug poisonings followed by sedatives/hypnotics/antipsychotics (9.3%), antidepressants (7.3%), and cardiovascular drugs (6.5%) [21]. According to data obtained from World Health Organization (WHO), unintentional poisonings claimed the lives of an estimated 193,460 people worldwide in 2012, and the majority of the deaths (84%) were in low- and middle-income countries. Suicide causes the loss of a million people each year and environmental chemicals such as pesticides lead to a significant number deaths annually. It is estimated that deliberate ingestion of pesticides causes 370,000 deaths each year. The problem is getting worse with time as newer drugs and chemicals are developed in vast numbers. On the other hand, snakebites are a largely underappreciated public health problem in many countries and they lead to significant challenges for medical care. While reliable data are hard to obtain, WHO estimated that about 5 million snakebites and 2.5 million envenomings occur each year. As antivenoms are not present in many parts of the world, snake venoms cause at least 100,000 deaths, 300,000 amputations, and many permanent disabilities [22].

Poisoning due to accidental or deliberate ingestion or inhalation of drugs or chemicals is a common, acute medical emergency. For a seriously poisoned patient, a hospital emergency room serves as the initial phase of treatment. For optimal care and treatment of a poisoned patient, clinical toxicologists usually recommend a methodically executed and stepwise approach. The six main steps of the initial clinical encounter for a poisoned patient are: (i) stabilization, (ii) clinical evaluation, (iii) prevention of absorption, (iv) enhancement of elimination, (v) administration of antidote, and (vi) supportive care and clinical follow-up [23–26].

4. Antidotes

An antidote is a substance that can counteract a form of poisoning. There is relatively small number of specific antidotes available for clinical use as it is difficult to develop a specific antidote and the market is very narrow. Furthermore, performing clinical trials in overdose patients have also practical difficulties. Although the Food and Drug Administration (FDA) forces drug companies to develop antidotes through the Orphan Drug Act, there is still need for safer and more specific antidotes today as many antidotes in use have a relatively low margin of safety or therapeutic index [27].

Antidotes have various modes of actions. Some are competitive receptor antagonists (e.g., naloxone, and flumazenil), while some are competitive receptor agonists (e.g., adrenaline and physostigmine). Some antidotes act as competitive enzyme antagonists (e.g., ethanol). Some act as chelating agents and they are mostly used against intoxication with metals [British anti-Lewisite (BAL) and succimer for lead, desferrioxamine for iron, cobalt edetate for cyanide, and calcium for fluoride]. Some antidotes reverse toxic effects on target molecules (glucagon and octreotide), while some use physiological antagonism (benzodiazepines). In some cases, antidotes pharmacologically antagonize the effects of the toxin/toxicant. Antidotes that bind to venoms or toxins are called “antivenoms.” The antidote can also facilitate the body clearance of the toxin/toxicant and it is possible for certain chemicals to exert their antidote effects by chemically reacting with biological systems in order to increase the detoxifying capacity for the toxin/toxicant. In order to optimize the treatment of the poisoned patient, medical toxicologists must have detailed knowledge on the therapeutic use of antidotes and when to use them [28, 29].

5. Conclusion

Medical toxicology is an important field of medicine dedicated to the evaluation and treatment of poisoned and envenomated patients. Medical toxicologists mainly investigate the adverse health effects of medications, occupational and environmental toxins, and biological agents and specialize in the preventing, evaluating, treating, and monitoring an injury or illness from toxic exposure.

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Medical toxicologists can work in a variety of settings including emergency departments, inpatient units, outpatient clinics, occupational health settings, national and regional poison control centers, academic institutions, industry, commerce, governmental agencies, and clinical and forensic laboratories to serve for public health. Medical toxicology will a more important area of toxicology in the future, as FDA has approved 20–25 new drugs per year in the past two decades and annual approvals in the past 5 years have been in the range of 40–50 new drugs, except for a dip in 2016. Moreover, thousands of chemicals, household products, and cosmetics are introduced to the market every year. Newer, safer, and more effective antidotes should be available. Therefore, medical toxicologists should also put effort on finding antidotes for both old and new drugs as well as for environmental chemicals, toxins, and venoms. Poison control centers should also be more active and effective, particularly in developing countries, in order to reduce emergency hospitalizations and increase the quality of life.

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