POISONS, VENOMS AND TOXINS

Koh, Dawn Chin Ing, Tok Pei Loo, Chai Siaw Ching, Arunmozhiarasi Armugam and **Kandiah Jeyaseelan.**
Department of Biochemistry, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

Dannandan Jeyaseelan
Box Hill Hospital, Nelson Road, Box Hill, Victoria 3128, Australia.

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Summary

Poison is defined as a substance that when introduced into a living organism causes injury, illness or death by chemical reaction or other activity on the molecular scale. Some poisons are also toxins, usually referring to naturally produced substances that act as poisons in small quantities. Animal toxins that are collected in specialized apparatus and delivered subcutaneously (e.g. by sting or bite) are called venoms. The living organisms that carry poisons are called poisonous organisms. They could be poisonous plants or venomous/poisonous animals found either on land or in water. Poisons can be broadly classified as physical, chemical or biological agents. In this chapter, we have attempted to review some important poisons, venoms and toxins and have highlighted

their importance in medicine as potential therapeutic agents.

1. Introduction

A medieval physician, Paracelsus (1493-1541) stated: "All things are poisonous and there is nothing without poison. Solely the dose determines that a thing is not a poison". His words summed up one of the most important concepts in modern toxicology, that is, the dose makes the poison. A poison is thus defined as any physical or chemical agent that inflicts injury or even death on living organisms. Living organisms that carry poisons are called poisonous organisms. They could be poisonous plants or venomous/poisonous animals found either on land or in water.

The terms "venomous" and "poisonous" are often used synonymously but they have distinct meaning. A venomous animal is equipped with a set of special apparatus such as a venom gland and hollow hypodermic teeth or stingers for synthesizing and delivering its venom. Venom usually contains a cocktail of poisons and other organic substances that may facilitate the penetration and spreading of the poisons from the site of introduction. Venomous animals commonly use their venoms for capturing and digesting their prey. They can also utilize the venoms for defensive purposes. Poisonous plants and animals on the other hand lack such specialized devices but their tissues are in part or entirely poisonous to predators. They may not have a role in aggressive defense mechanisms, but affect other animals when eaten or touched. Hence, a poisonous organism is one that is harmful to consume, but a venomous organism uses poison/venom to defend itself against predators. Poisonous plants and animals are often known to be extremely beautiful and bright with attractive colors.

A substance is considered toxic if it contains a poison or induces poisoning. The word toxic comes from "toxikon", which means "poison arrow" in ancient Greek. A toxin in a scientific context is a biologically produced substance that causes injury to the health of a living organism, typically by interacting with the biological molecules within a living cell. Toxicity (effect caused by toxins) may be acute (sudden as in a bee sting), chronic (gradual as in the Guam cycad toxin) or both. Many plants, animals and microorganisms generate natural toxins to discourage or kill predators. Venoms contain both toxic and non-toxic components and a single organism can be both venomous and poisonous.

Ancient humans discovered poisons partly by witnessing the toxic effects at work by chance. They might have accidentally witnessed their fellow tribesman or animal being poisoned by a plant or another animal or mineral. The Egyptian manuscript known as the Ebers Papyrus, approximately 1500 B.C., speaks of products such as arsenic, lead, antimony, mandrake, hemlock, opium, aconite etc. that were known for their poisonous properties even at that time.

As early as 16,000 B.C., the Masai tribe of Kenya used poisons in darts and arrows so that their weapons were lethal enough to assure them a good harvest in their hunting trips. Among those arrow tip toxins was strophanthin, a cardiotoxic agent derived from plants indigenous to Kenya. However, ancient use of poisons was not limited to hunting. Some poisons were used as an alleged means of deciding if the accused was guilty of a crime. If the accused survived the ordeal, it was taken to mean that the gods were

affirming his innocence.

Modern Toxicology is characterized by extremely sophisticated scientific investigations and evaluation of toxic exposures of all kinds. Modern analytical methods allow detection of minute quantities of poison and are capable of extreme specificity so that compounds can be implicated in poisoning episodes to the near exclusion of others. The most important factor determining toxicity of a substance is its dosage. In studies of acute toxicity, LD_{50} is the main statistic used to compare the toxicity of a given substance. LD means" lethal dose", and the subscript 50 means that dose of toxicant which is acutely lethal to 50% of test organisms under controlled laboratory conditions. The units of LD_{50} are usually mass of chemical per kilogram of body weight (eg. mg/kg BW) of the organism. If the LD_{50} is smaller, a very little amount of the poison will be needed to kill 50 % of organisms and the poison will be considered to be highly toxic. At one end of the spectrum, water, which has a LD_{50} greater than 25g/kg (in mice) is generally classified as a substance which is essentially safe, while at the other end, botulinum toxin, which has a LD_{50} value of 0.00001 mg/kg, has the notorious reputation of being one of the most acutely lethal chemicals known to man. However, LD_{50} is by no means adequate for an in-depth understanding of poisons. Firstly, LD_{50} describes only one end point, death, and we are more than often exposed to toxicants at concentrations well below LD_{50}. There exist many other undesirable outcomes of exposure to toxicants such as organ failure, cancer, infertility and even aberrations in behavior. The duration of exposure, as well as the frequency of exposure to a specific toxicant, adds another dimension to toxicology. For instance, it takes more than a single exposure of ultraviolet radiation for one to develop skin cancer. Most skin cancers occur late in life as a result of cumulative UV exposure from childhood onwards and even then, there are other factors influencing the outcome of the exposures such as genetic susceptibility to cancer. LD_{50} values are derived mainly from studies done on rats and other rodents. These LD_{50} values may not truly reflect the toxicity of the substances to humans, though in most circumstances, they are fairly good approximations. Dioxin is an unwanted side product from the production of materials involving phenols and chlorine. The LD_{50} of dioxin for guinea pigs is about 6μg/kg while that for hamsters is 3mg/kg. When a chemical plant exploded in Seveso, Italy, in 1976, clouds of dioxin descended upon surrounding areas. While many farm animals died following the exposure, humans experienced low level effects such as chloracne, a severe skin rash. At least in terms of acute toxicity, a specific substance may produce different toxicities in different species. Lastly, to make matters more complex, even within a species there are differences in these toxic responses, depending on the gender, age, nutritional and health status, genetic susceptibility and even the presence of synergists or antagonists within an individual. Toxicokinetics is useful in explaining these inter-individual differences in toxic responses and can have a significant impact on the management of patients. Toxicokinetics refers to the body's handling of toxins in four major areas: absorption, distribution, metabolism and elimination.

It is obvious that the route of absorption of poison into the body affects its toxicity. An excellent example is the phenomenon of first-pass metabolism. Some drugs such as morphine and heroin are strongly taken up and metabolized to the point of being fully metabolized in their first pass through the liver. Hence, these drugs would achieve low blood concentrations when administered orally, as they would reach the liver by the

portal system and would be fully metabolized before reaching systemic circulation. Such drugs would be more potent when administered intravenously rather than orally. The distribution of poisons is also critical to potency. An example is phenytoin, which is an anticonvulsant drug used in the treatment of epilepsy. Phenytoin is normally 10% free in blood, 90% of which is bound by blood protein, albumin. However, a patient with low albumin lacks adequate binding protein and can have a higher free fraction of phenytoin in plasma. There are also differences in the efficacies of metabolism of drugs among individuals. If a toxin is more rapidly degraded to non-toxic metabolites in an individual, it will be less toxic compared to others with a lower metabolic rate. Newborns for instance, generally have lower efficacies of metabolism of drugs, thus they can be intoxicated by a low dose of toxicant that is harmless to adults. The liver and kidneys are the main excretory organs involved in the elimination of drugs and toxins. If the liver function is impaired in an individual with chronic alcoholic abuse, then a drug that relies primarily on hepatic elimination will be poorly excreted and can accumulate to toxic levels within the body.

2. Categories of Poison

Ancient humans made primitive attempts to classify poisons. Poisons were divided into those that are slow-acting, such as arsenic, versus those that are fast-acting, such as strychnine. Dioscorides, a Roman physician, divided poisons according to their origin as vegetable, mineral, or animal. In modern times, poisons are classified according to the physiological system on which they predominantly exert their effects. For instance, a category of such classification is cardiotoxic agents, which exert toxic effects on the heart. But this form of classification may be too restrictive for toxicants which exert effects on multiple systems. Another method of classification is to group the toxicants into general categories such as metals, alcohols, drugs of abuse etc. In this chapter, we group the toxicants under three main categories as physical, chemical and biological agents (Figure 1).

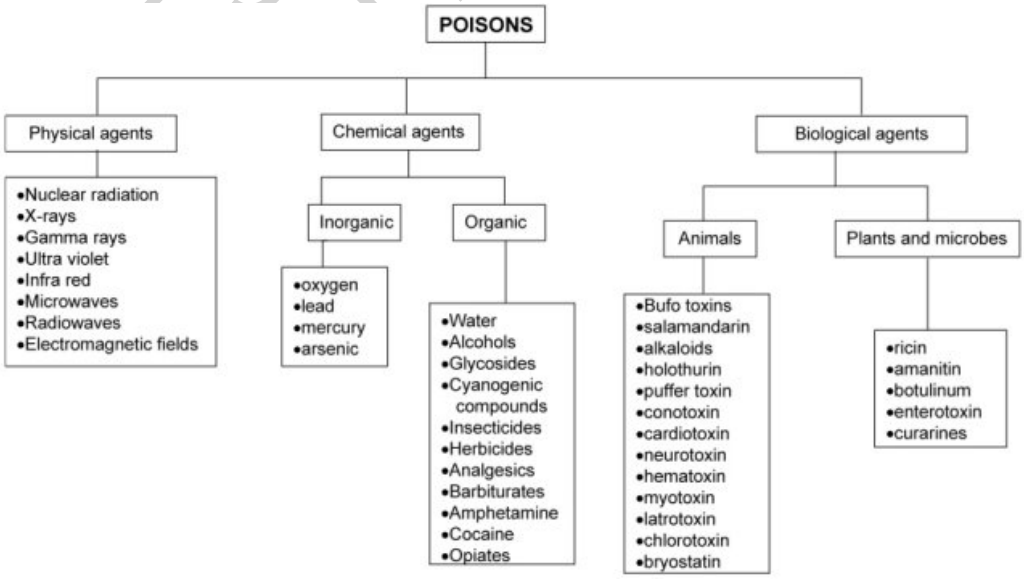

Figure 1. Categories of Poison

2.1. Physical Agents

Among the physical toxicants, radiation is an established carcinogen. The supporting evidence is so voluminous that only two are presented. The dropping of atomic bombs on Hiroshima and Nagasaki was a landmark event in World War II. Follow-up of the survivors revealed a significantly increased incidence of leukemia after an average latent period of about seven years. Even decades later, leukemia risk for individuals heavily exposed to the radiation is still above the level for control populations. Another example is the nuclear power accident at Chernobyl in the former Soviet Union that continues to exact its toll in the form of high cancer incidence in surrounding areas.

Radiation is of two major types, ionizing and non-ionizing. The increased cancer incidence following the Chernobyl nuclear accident and the Hiroshima and Nagasaki bombings was due to ionizing radiations. Ionizing radiation can be in the form of X-rays and gamma rays, high energy neutrons, α particles or β particles. Generally, 88% of our radiation exposure is due to natural sources. Manmade sources of ionizing radiation, making up the remaining 12%, include medical X-ray investigations, operations of nuclear power plants, production of nuclear weapons, etc. Ionizing radiation exerts its toxicity mainly by the production of free radicals known as reactive oxygen species (ROS). Free radicals are highly reactive, each with a single unpaired electron and they cause destruction by scavenging electrons from biologically important molecules in the cells and hence undermining the integrity of these molecules. For example, ROS may result in DNA damage by scavenging electrons from thymidine, a type of nitrogenous base in DNA, to cause single-stranded breaks in DNA. Irreparable DNA damage induces apoptosis, that is, programmed cell death. Such cell death, which is not part of the normal 'development plan', can result in structural malformations, especially in young embryos or developing fetuses. That is why it is important for physicians to ascertain that female patients are not pregnant before sending them for a medical X-ray. Cellular damage due to ionizing radiation can also induce tumor formation. This happens when the gene encoding for p53 is mutated. p53 prevents tumor formation and is referred to as the guardian of our genome. When p53 is defective as a result of mutation of its gene, the check on tumor formation is removed. This briefly explains the higher cancer incidence in populations that have been intensely exposed to ionizing radiation.

Non-ionizing radiation may take the form of ultraviolet (UV), visible light, infrared, microwaves and radio waves, and extremely low frequency electromagnetic fields. Sources of extremely low frequency electromagnetic fields are power lines and video display terminals, such as the monitors used with computers. There is concern that extremely low frequency electromagnetic fields could cause adverse health effects, such as childhood cancers, however the evidence remains controversial. In contrast, the toxic effects of UV radiation are more recognized.

Ultraviolet rays are of three general types, UVA (long wave UV), UVB (middle wave UV) and UVC (short wave UV). Sources of ultraviolet rays include sunlight (generally considered as the most important source), sunlamps and sunbeds (used in tanning booths and tanning salons). These UV rays are generally UVA and UVB types. UVC rays are not normally encountered by most people, except in certain occupations such as

laboratory work and arc-welding and are potentially dangerous. Exposure to UV radiation from sunlight is associated with the development of three types of skin cancer: basal cell carcinoma, squamous cell carcinoma, and malignant melanoma. Those at greatest risk are people who live in locales receiving a great deal of sunlight, such as in Australia and New Zealand. Non-melanoma cancers are associated with cumulative exposure to UV radiation throughout one's lifetime, whereas melanoma cancers are associated with intense intermittent exposure e.g. in sunbathing. UV radiation may cause tumor formation by a mechanism similar to that of ionizing radiation by inactivating p53. UV radiation has also been implicated in chronic damage to skin such as premature wrinkling, aging and dryness and in damage to the immune system and eyes. Although UV radiation is toxic, controlled doses can be harnessed in UV therapy for psoriasis, a chronic and recurring skin disorder characterized by scaling of the skin. This is an example of how a toxicant that undermines health can sometimes be used in treating diseases.

2.2. Chemical Agents

Chemical agents can range from anything as seemingly innocuous as water and oxygen to acutely lethal organophosphates and heavy metals.

Water can cause toxicity among athletes participating in long distance running. This is due to excessive dilution of sodium levels within the body, especially during excessive drinking of water. It may manifest as a mild headache but in a more severe state, it can result in collapse. It has now been suggested that rapid assessment of serum sodium levels should be undertaken before proceeding to subsequent emergency steps. This is important because a person who collapses due to dehydration may present in a similar manner as one who suffers from over hydration. For dehydration cases, hydration steps would be undertaken. If a patient suffering from over hydration is mistakenly identified as suffering from dehydration, then incorrect resuscitation steps would result in worsening the condition of water intoxication in the patient.

Oxygen, which is essential to our survival, can actually cause toxicity in divers. As divers progress to deeper depths, pressure of gases increases, though the oxygen concentration remains the same. At sea level, oxygen pressure is about 0.21 atmospheres. When oxygen pressure reaches more than 0.50 atmospheres during diving, lung damage is incurred. When oxygen pressure reaches more than 2.0 atmospheres, especially during exertion, divers may suffer a convulsion, resembling an epileptic seizure. Similar effects will also be seen if the oxygen content of the air we breathe increases beyond 21%. In fact, we cannot survive in a pure oxygen environment.

2.2.1. Metals as Poisons

Metals are found abundantly in nature. They have long been seen as potential candidates for poisons and for other uses. It is no wonder that the history of metals as poisons dates back to ancient times.

Lead was "one of the seven metals of the ancient world". Massive use of lead occurred most notably in the Roman Empire. Water was transported in lead-lined channels and

lead acetate, called the sugar of lead, was deliberately added to wine to enhance its taste and to prevent spoiling. In fact, toxicity of lead can be seen in its preservative effects, where it inhibits enzymes of microbes and thus their proliferation. Indeed, lead also exerts its toxicity in humans via a similar mechanism. At the peak of the Roman Empire, lead production was estimated at over 80,000 tons per year. Some historians believe that the Romans were greatly weakened by chronic lead poisoning and that this contributed significantly to the eventual downfall of the Roman Empire.

Mercury has been featured in history as a double edged sword due to its ability to both kill and heal. Such properties of mercury were well featured in the assassination of Benvenuto Cellini, one of the giants of the Italian Renaissance. Cellini was well recognized as an unsurpassable sculptor of his times. Unfortunately, he contracted a severe case of syphilis at the age of 29. Cellini refused the conventional treatment of mercury and used Guaiac (which was alleged to cure syphilis). But his condition deteriorated. His enemies, who were eager to get rid of him, invited him over for dinner where he was heavily poisoned with mercury. Cellini had a close shave with death, with his intestines badly corroded. However, Cellini recovered from the poisoning and also recovered from syphilis. Cellini's poisoners had unintentionally exposed him to a sub-lethal dose of mercury, which was toxic enough to kill the *Treponema* parasite in his body (that causes syphilis).

Arsenic is well featured in the history of crime. Ironically, one of the most famous episodes, the murder of Napoleon Bonaparte, may not have actually been a case of arsenic poisoning. Napoleon was imprisoned by the British on the island of St Helena, where he grew weaker by the day. Napoleon was convinced that he was being chronically poisoned by his British jailers. Modern day testing of Napoleon's hair (which had amazingly survived two centuries) detected arsenic, however subsequent testing revealed mixed results. Moreover, the finding of a large stomach carcinoma during Napoleon's autopsy was well-supported and seems to be a more likely cause of his gradual debilitation. Arsenic is rarely found as a pure element in nature. It is readily oxidized to form oxides, of which the most abundant is lead arsenate. However, trivalent arsenic trioxide, As_4O_6, is believed to be the specific agent most commonly employed in homicides. The most toxic form exists as arsine gas (AsH_3) which fortunately is rare. It is estimated that 80% of the industrial uses of arsenic are in the form of pesticides. For instance, sodium arsenite is employed as an ant bait. Arsenic from the environment and industry finds its way into our body through water and food. Acute arsenic poisoning causes abnormally large numbers of gastrointestinal cells to be sloughed off, giving a fine, white appearance in vomit. Arsenic inhibits the activity of proteins containing sulfhydryl groups, notably pyruvate dehydrogenase (an enzyme involved in the carbohydrate metabolism to yield energy currency, ATP). When this enzyme is inhibited, over 95% of ATP generation in the cells is impaired and this in turn impairs many ATP- dependent biochemical processes in the body. The consequence can be fatal for most, if not all bodily functions, which ultimately rely on ATP for energy. At sufficiently high doses, death would ensue and if not, severe liver and renal failure eventually occurs. Chronic arsenic poisoning differs markedly from acute arsenic poisoning. Chronic arsenic intoxication results in hair loss and a blush of skin known as milk rose. Indeed, ancient women have used arsenical cosmetics in pursuit of beauty.

2.2.2. Alcohols - Delicious Poisons

Low molecular weight alcohols are commonly encountered in a clinical setting. These include methanol, ethanol, isopropanol and ethylene glycol. One of the major effects of alcohol is sedation of the central nervous system (CNS). The blood brain barrier of the central nervous system is considerably less permeable to polar substances than to non-polar ones. Alcohols are generally polar molecules, with their polarity being attributed to their hydroxyl groups. At high molecular weights (MW), the net polarity of the alcohol declines and hence it becomes more able to permeate the CNS and exert its toxic effect. The exception is methanol, which despite being relatively more polar than other mono-hydroxyl alcohols, is also more toxic.

Methanol is a common industrial solvent with applications as a paint thinner, anti-freeze, brake fluid, and many other uses. Methanol is oxidized within liver cells in two stages. It is converted to formaldehyde by alcohol dehydrogenase and then to formic acid by aldehyde dehydrogenase. Formic acid causes metabolic acidosis. In addition, formic acid reduces aerobic respiration resulting in the production of lactate, which aggravates the existing acidosis. In severe poisoning, vision is affected because retinol dehydrogenase, an enzyme involved in normal vision, oxidizes methanol to formaldehyde. Formaldehyde, being neurotoxic, mediates vision impairment by causing degeneration of the optic nerve.

Interestingly, ethanol is used as a semi-antidote for methanol poisoning, as it is able to compete with methanol for substrate sites on the enzyme alcohol dehydrogenase. Because the enzyme binds to ethanol with greater affinity than for methanol, when both methanol and ethanol are at the same concentrations, ethanol can effectively reduce the toxicity of methanol. However, because ethanol is also potentially neurotoxic, its administration as an antidote must be limited in dose.

Ethylene glycol is a major ingredient in automotive antifreeze. It is a colorless, somewhat viscous and sweet-tasting liquid. There are many case reports of children being poisoned as a result of consuming ethylene glycol. Ethylene glycol is metabolized sequentially through a metabolic pathway to oxalate. Oxalate chelates Ca^{2+} and causes hypocalcemia, that is, low serum Ca^{2+} levels. This can cause tetany of respiratory muscles. The resulting calcium oxalate crystals can also be deposited in organs such as the kidneys, causing mechanical damage to them. Severe metabolic acidosis can also result in coma.

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Biographical Sketches

K. Jeyaseelan is currently a Professor in Biochemistry and Molecular Biology at the Department of Biochemistry and a Senior Professor at the National University of Singapore Graduate School for Integrative Sciences and Engineering. He has been working in the field of Biomedical Sciences, especially on molecular toxinology and toxicogenomics, for more than 15 years. He received his post-graduate training in England and the Netherlands and has held several research, academic and administrative positions in Universities. He is also a Fellow of the Institute of Biology (London). He has more than 100 publications in international peer-reviewed journals and books and has more than 200 complete gene and protein sequences deposited in the databases at the National Centre for Biotechnology Information (NCBI), National Institute of Health, USA.

Ms Dawn Koh Chin Ing (B.Sc Hons) is a final year Ph.D student attached to Professor Jeyaseelan's laboratory.

Ms Tok Pei Loo is a third year (undergraduate) medical student at the NUS School of Medicine.

Dr Dannandan Jeyaseelan (M.B.B.S, Monash) is a practicing medical doctor from Box Hill Hospital, Melbourne, Australia.

Ms Chai Siaw Ching (B.Sc) and **Dr Arummozhiarasi Armugam** (MSc, Ph.D) are Senior Laboratory Officer and Senior Research Fellow respectively from Professor Jeyaseelan's laboratory.