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A REVIEW ON TOXICOLOGY

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ABSTRACT

The therapeutic outcome of cisplatin is limited due to its adverse side effects in normal tissues. Despite its potent antineoplastic effect, cisplatin is known by a relevant collateral action, for instance, acute renal failure. The aim of this study was to assess the effectiveness of Pituranthos chloranthus (PC) essential oil for contracting cisplatin-induced toxicity, in Balb/c mice. The standard mouse model of cisplatin-induced acute kidney injury (AKI), consisting of one intraperitoneal injection of cisplatin (20 mg/kg), was adopted. Mice were pretreated by intraperitoneal administration of PC (5 and 10 mg/Kg b.w) for one week. Cisplatin induced alteration in renal and liver functions, evidenced by increased serum biomarkers levels (creatinine, ALT, and AST). Significant mitigation of cisplatin-induced toxicity was confirmed by lowered levels of serum biomarkers and reduced DNA damage in liver and kidney. PC also restored the alterations in oxidative stress markers and proinflammatory cytokine IFN-? level. Overall, this study provides, for the first time, that PC can be applied as an antioxidant-adjuvant treatment to mitigate cisplatin-induced renal failure

INTRODUCT

Toxicity testing is paramount in the screening of newly developed drugs before it can be used on humans. Toxicity testing is the determination of potential hazards a test substance may likely produced and the characterization of its action, most of the toxicity testing is carried out on experimental animals.The advantages of using animal models in toxicity testing are enormous. These advantages include the possibility of clearly defined genetic constitution and their amenity to controlled exposure, controlled duration of exposure, and the possibility of detailed examination of all tissues following necropsy.. The information obtained can serves as the basis for hazard classification and labeling of chemicals in commerce[.The essence of toxicity testing is not just to check how safe a test substance is; but to characterize the possible toxic effects it can produce. Toxicity testing was given much attention following early 1960s thalidomide

catastrophe; with thousands of children born worldwide with severe birth defects2. After this incidence many countries of the world have resolved to go for toxicity testing and teratogenicity in both sexes so as to prevent further tragedies.

Importance of toxicity studies

1.To establish a dose response curve.

2.TO ensure safety of new chemicals for use as pesticides, drugs, or food additives before they are registered for general use in industry or doctors clinics.

3.To produce epidemiological studies to explain observations in the population, for instance, the long investigation into the association of smoking with lung To validate new methods of testing or investigation, particularly those conducted in vitro rather than in animals.

4.To establish the mode of action or mechanism for a toxic effect that may have been seen in other studies.

The two basic principles guiding toxicity test in animals

Toxicity studies are divided into:

1.Acute toxicity studies

To check the effect of the test substances on laboratory animals and its direct toxic effect on human. Exposure of laboratory animals to high doses in order to evaluate its possible hazard on human that are exposed to much lower doses This is a short term assessment and evaluation of potential hazard test substance or consequences of single dose of a test substance.Acute toxicity testing may be used in risk assessments of chemicals for humans and non-target environmental organisms. Acute toxicity study is better described as LD5(), which is defined as the dose which kills 50% of animals. LD5() is used for the estimation of the toxicity of the chemical agents. Acute toxicity provides guidelines on the dose to be use in more prolonged studies and it also provides the basis for which other testing program can be design. In acute toxicity studies rodent are mostly used because they are economical and readily available and easy to handle. This test is carried out in each species of animal as the same route as intended to be use in treatment.

Importance of acute toxicity testing

To identify the target organ of toxicity.

To provides safety measures and monitoring guild lines for workers involved in the development and testing of test substances.

To provides information needed for the dose selection in prolonged toxicity studies.

To generate data containing the adverse effects of a substance on human, animal health and environment. To provides the basis for which other testing program can be design.

For academics and regulating purpose; classification, labelling and transportation of chemical agents

2.Sub-acute toxicity studies

This study is conducted to determine organs affected by different dose levels. This study access the nature of toxic dose under more realistic situation than the acute toxicity studies. Three dose levels are normally used. Dose that is high enough to elicit definite signs of toxicity but not to kill many of the animals.

Low dose that is expected to induce no toxic effect.

Intermediate dose

Doses are generally selected on the basis of information obtained in acute toxicity studies using both LD50 and the slope of the dose response curve. The duration of sub-acute toxicity studies depend on intended duration of the test substance.

Chronic toxicity studies

This study is basically to determine the organs affected and to check whether the drug is potentially carcinogenic or not. This test extends over a long period of time and it involves large groups of laboratory animals. Chronic toxicity is the development of adverse effects as the result of long term exposure to a toxicant or other stressor. It can manifest as direct lethality but more commonly refers to sublethal endpoints such as decreased growth, reduced reproduction, or behavioral changes such as impacted swimming performance.

Common aquatic chronic toxicity tests

Chronic toxicity tests are performed to determine the long term toxicity potential of toxicants or other stressors, commonly to aquatic organisms. Examples of common aquatic chronic toxicity test organisms, durations, and endpoints include:

- Fathead minnow, Pimephales promelas, larval survival and growth
- Daphnia, Daphnia magna, 21 -d survival and reproduction
- Green algae, Raphidocelis subcapitata, 72-h growth
- Amphipod, Hyalella azteca, 42-d survival, growth, and reproduction

GENOTOXICITY AND MUTAGENICITY- TERATOGENICITY

- Genotoxicity covers a broader spectrum of endpoints than mutagenicity, includes DNA damage assessments. DNA damage are not themselves necessarily transmissible to the next generation of cells, pre-mutagenic
- Mutagenicity refers to the production of transmissible genetic alterations. Somatic cell genotoxicity may lead to cancer. Germ cell genotoxicity may lead to infertility or diseased children

TERATOGENICITY C

Capacity of a drug to cause foetal abnormalitites when administered to the pregnant mother. C Placenta does not consider a strict barrier and any drug can cross it to a greater or lesser extent. The embryo is one of the most dynamic biological systems

- Genotoxicity Genotoxicity tests can be defined as in vitro and in vivo tests designed to detect compounds that induce genetic damage by various mechanisms.
- These tests enable hazard identification with respect to damage to DNA and its fixation. Genotoxins can be of the following category depending on its effects

  I) Carcinogens or cancer causing agents

  2)Mutagens or mutation causing agents

  3)Teratogens or birth defect causing agents. Agents that can cause direct or indirect damage to the DNA o Reactive oxygen species. UV and ionizing radiations. o Nucleoside analogues o Topoisomerase inhibitors . o Protein synthesis inhibitors .

OECD GUIDELINES . Genetic Toxicology : was first published in 1987 .Following a global update of the Genetic Toxicology o Latest revision provides (I) general background and historical information on the OECD genetic toxicology. (2) a brief overview of the important types of genetic damage evaluated by these tests. (3) a description of the specific tests.

SCHEDULE -Y . Gene mutation in bacteria

- An in-vitro test with cytogenic evaluation of chromosomal damage
- An in-vivo test for chromosomal damage using rodent hematopoietic cells (chromosomal aberration , micronucleus o DNA adduct tests , DNA strands break DNA repair /recombination.

ICH . S2A:Guidance on Specific aspects of Regulatory Tests for Pharmaceuticals

S2B: Standard Battery for Testing of Pharmaceuticals .

M3:Timing of PreClinical Studies in Relation to Clinical Trials.

❖ Importance Genotoxicity assays have become an integral component of regulatory requirement.

- Compounds which are positive in these tests, have the potential to be human carcinogens and/or mutagens. so it's used in prediction.

Aim : To identify substances that can cause genetic alterations in somatic and/or germ cells.

- To identify substances that causes genetic alterations and thus use this information in regulatory decisions.

Mechanism of Genotoxicity

- The damage to the genetic material is caused by the interactions of the genotoxic substance with the DNA structure and sequence.
- These genotoxic substance interact at a specific location or base sequence of the DNA structure causing lesions, breakage, fusion, deletion, mis-segregation or non- disjunction leading to damage and mutation .

Standard test battery for genotoxicity

AMES TEST (Bacterial reverse mutation test) Bacteria Salmonella typhimurium or strains E.coli.

Ames test was brought forward by Bruce Ames in 1970. o He is professor in university of California , berkely . In department of biochemistry. o He developed this method because previous methods were expensive and time consuming.

Principle : Identifies substances that induce gene mutations by base substitutions or frame-shifts.

- Two species of bacteria Salmonella typhimurium and Escherichia coli with identified mutations in an amino acid i.e. His or Trp as the reporter locus.
- It detects mutations which revert mutations present in the test strains and restore the functional capability of the bacteria to synthesize an essential amino acid PROCEDURE 2 methods : I.PIate incorporation method. 2. pre-incubation method.

STEPS OF AMES TEST: Prepare the culture of Salmonella histidine auxotroph's (His-). o Mix the bacterial cells and test substance in dilute molten top agar with a small amount of histidine in one set, and control with complete treated animals is an indication of induced chromosome damage because they lack main nucleus

INVITRO MAMMALIAN CHROMASOMALABBERATION TEST PRINCIPLE:

- After exposure of cell cultures , treated with a metaphasearresting substance colchicine . with and without metabolic activation
- harvested, stained and metaphase cells are analysed microscopically for the presence of chromosome aberrations . Cell lines: CHO, CHL, V79, TK6. Structural aberrations may be of two types: chromosome or chromatid.

MAMMALIAN BONE MARROW CHROMOSOME ABERRATION TEST

principle : For the detection of structural chromosome aberrations induced by test compounds only in bone marrow cells of animals (rodents).

Animals are exposed to the test substance , metaphase-arresting agent , sacrificed at appropriate times after treatment.

- Bone marrow cells are usually obtained from the femurs or tibias immediately after sacrifice , and stained using established methods.
- Blood :tail vein or other appropriate blood vessel , smear preparations are made and then stained . DNA specific stain [e.g acridine orange or Hoechst 33258 plus pyronin-Yl

Prior to sacrifice, animals are injected i.p with an appropriate dose of a metaphase arresting agent , sampled thereafter. Cells are harvested from the bone marrow and analysed from chromosome aberrations. o Chromosome preparation: bone marrow in hypotonic solution , spread on slides and stained General Principles In Treatment of Poisoning

- ✓ GENERAL PRINCIPLES OF TREATMENT OF POISONING,
- ✓ CLINICAL SYMPTOMS AND MANAGEMENT OF BARBITURATES, MORPHINE,
- ✓ ORGANOPHOSPHOSPHORUS COMPOUND
- ✓ LEAD, MERCURY AND ARSENIC POISONING.

General Principles of Poisoning

Poisoning is contact with a substance that results in toxicity. Symptoms vary, but certain common syndromes may suggest particular classes of poisons. Diagnosis is primarily clinical, but for some poisonings, blood and urine tests can help. Treatment is supportive for most poisonings; specific antidotes are necessary for a few. Prevention includes labeling drug containers clearly and keeping poisons out of the reach of children. Most poisonings are dose-related. Dose is determined by concentration over time. Toxicity may result from exposure to excess amounts of normally nontoxic SubstancesPoisoning is distinguished from hypersensitivity and idiosyncratic reactions, which Some poisonings result from exposure to substances that are poisonous at all doses. are unpredictable and not dose-related, and from intolerance, which is a toxic reaction to a usually nontoxic dose of a substance.

Poisoning is commonly due to ingestion but can result from injection, inhalation, or exposure of body surfaces (eg, skin, eye, mucous membranes). Many commonly ingested nonfood substances are generally nontoxic

Table: Substances Usually Not Dangerous When Ingested however, almost any substance can be toxic if ingested in excessive amounts.

Accidental poisoning is common among young children, who are curious and ingest items indiscriminately despite noxious tastes and odors; usually, only a single substance is involved. Poisoning is also common among older children, adolescents, and adults attempting suicide; multiple drugs, including alcohol, acetaminophen, and other OTC drugs, may be involved. Accidental poisoning may occur in the elderly because of confusion, poor eyesight, mental impairment, or multiple prescriptions of the same drug by different physicians (see also After exposure or ingestion and absorption, most poisons are metabolized, pass through the GI tract, or are excreted. Occasionally, tablets (eg, aspirin, iron, enteric-coated drugs) form large concretions (bezoars) in the GI tract, where they tend to remain, continuing to be absorbed and causing toxicity.

Symptoms and Signs:

Symptoms and signs of poisoning vary depending on the substance .

Symptoms and Treatment of Specific Poisons . Also, different patients poisoned with the same substance may present with very different symptoms. However, 6 clusters of symptoms (toxic syndromes, or toxidromes) occur commonly and may suggest particular classes of substances Common Toxic Syndromes (Toxidromes). Patients who ingest multiple substances are less likely to have symptoms characteristic of a single substance.

Symptoms typically begin soon after contact but, with certain poisons, are delayed. The delay may occur because only a metabolite is toxic rather than the parent substance (eg, methanol, ethylene glycol, hepatotoxins). Ingestion of hepatotoxins (eg, acetaminophen, iron, Amanita phalloides mushrooms) may cause acute liver failure that occurs one to a few days later. With metals or hydrocarbon solvents, symptoms typically occur only after chronic exposure to the toxin.

Ingested and absorbed toxins generally cause systemic symptoms. Caustics and corrosive liquids damage mainly the mucous membranes of the GI tract, causing stomatitis, enteritis, or perforation. Some toxins (eg, alcohol, hydrocarbons) cause characteristic breath odors. Skin contact with toxins can cause various acute cutaneous symptoms (eg, rashes, pain, blistering); chronic exposure may cause dermatitis.

Inhaled toxins are likely to cause symptoms of upper airway injury if they are water-soluble (eg, chlorine, ammonia) and symptoms of lower airway injury and noncardiogenic pulmonary edema if they are less water-soluble (eg, phosgene). Inhalation of carbon monoxide, cyanide, or hydrogen sulfide gas can cause organ ischemia or cardiac or respiratory arrest. Eye contact with toxins (solid, liquid, or vapor) may damage the cornea, sclera, and lens, causing eye pain, redness, and loss of vision. Some substances (eg, cocaine, phencyclidine, amphetamine) can cause severe agitation, which can result in hyperthermia, acidosis, and rhabdomyolysis.

Diagnosis:

- Consideration of poisoning in patients with altered consciousness or unexplained symptoms
- History from all available sources
- Selective, directed testing

The first step of diagnosis of poisoning is to assess the overall status of the patient. Severe poisoning may require rapid intervention to treat airway compromise or cardiopulmonary collapse.

Poisoning may be known at presentation. It should be suspected if patients have unexplained symptoms, especially altered consciousness (which can range from agitation to somnolence to coma). If purposeful self-poisoning occurs in adults, multiple substances should be suspected.

History is often the most valuable tool. Because many patients (eg, preverbal children, suicidal or psychotic adults, patients with altered consciousness) cannot provide reliable information, friends, relatives, and rescue personnel should be questioned. Even seemingly reliable patients may incorrectly report the amount or time of ingestion. When possible, the patient's living quarters should be inspected for clues (eg, partially empty pill containers, a suicide note, evidence of recreational drug use). Pharmacy and medical records may provide useful information. In potential workplace poisonings, coworkers and supervisors should be questioned. All industrial chemicals must have a material safety data sheet

Conclusion:PC treatment prior to cisplatin administration in mice can minimize cisplatin-induced nephrotoxicity, genotoxicity, and inflammation through enhancing oxidative status. &e current finding suggests the efficiency of PC as a potential agent for the development of cisplatin chemotherapy.

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