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AN OVERVIEW ON PESTICIDE POISON

Geetha Rani Valaparla, P.Priyanka, SK. Hanisha,T. Rajya Lakshmi, P.Alekhya

Department of pharmacy, A.M. Reddy memorial college of pharmacy, Petlurivaripalem, Narasaraopet, Palnadu (dt), 522601.

Corresponding authors details:

Geetha Rani Valaparla

Associate professor

Dept. Of pharmacology

A.M Reddy Memorial college of pharmacy,

petlurivaripalem,

Narasaraopet [522601],palnadu, AP

ABSTRACT:

Organochlorines are a substance derived from insecticides & it is classified into 3 types.Organochlorines are spread over crops then farmers inhale those pesticides and metabolized into their body.So that it leads to more side effect.

It is banned in US & other countries due to carcinogenic toxicity.The review explained about mechanism of action, symptoms of acute and chronic poison.Symptomatic management of organochlorines are gastric lavage, barbiturates/diazepam and avoid oils & epinephrine &cholestyramine.Carbamates are salt or esters containing the anion NH2COO- or the group -OOCNH2, derived from the hypothetical compound carbamic acid (Ethyl carbamate). The article represents the classification of the carbamates, physical appearance, toxicokinetics, and its fatal dose based on its level of toxicity is described. Carbamates mechanism of action in case of poisoning is explained and symptoms such as chest tightness, bronchospasm, weakness caused due to Poisoning. The diagnosis of carbamates can be done by some laboratory examinations such as X-ray, metabolites in urine. The antidote administration in carbamate poisoning is oximes. Carbamate typically have a more benign clinical course compared to other pesticide poisoning.Pyrithrins are natural insecticides produced by certain species of the chrysanthemum plant.The natural pyrithrins are contact poisons which quickly penetrate the nerve system of the insect.pyrithrins are used to spray inside the houses, which protect populations from malarial mosquito bites, cockroaches, beetles and flies.organic farmers can also use pyrithrins as an insecticide for fruits and vegetables.Human shorterm side-effects in sensitive individuals include eye, skin, throat, nose irritation and may

include breathing problems like aspiration pneumonia.This pyrithrin poisoning can be managed by decontamination of skin with soap and water. Gastric lavage is best avoided in the case of pyrithrin ingestion.

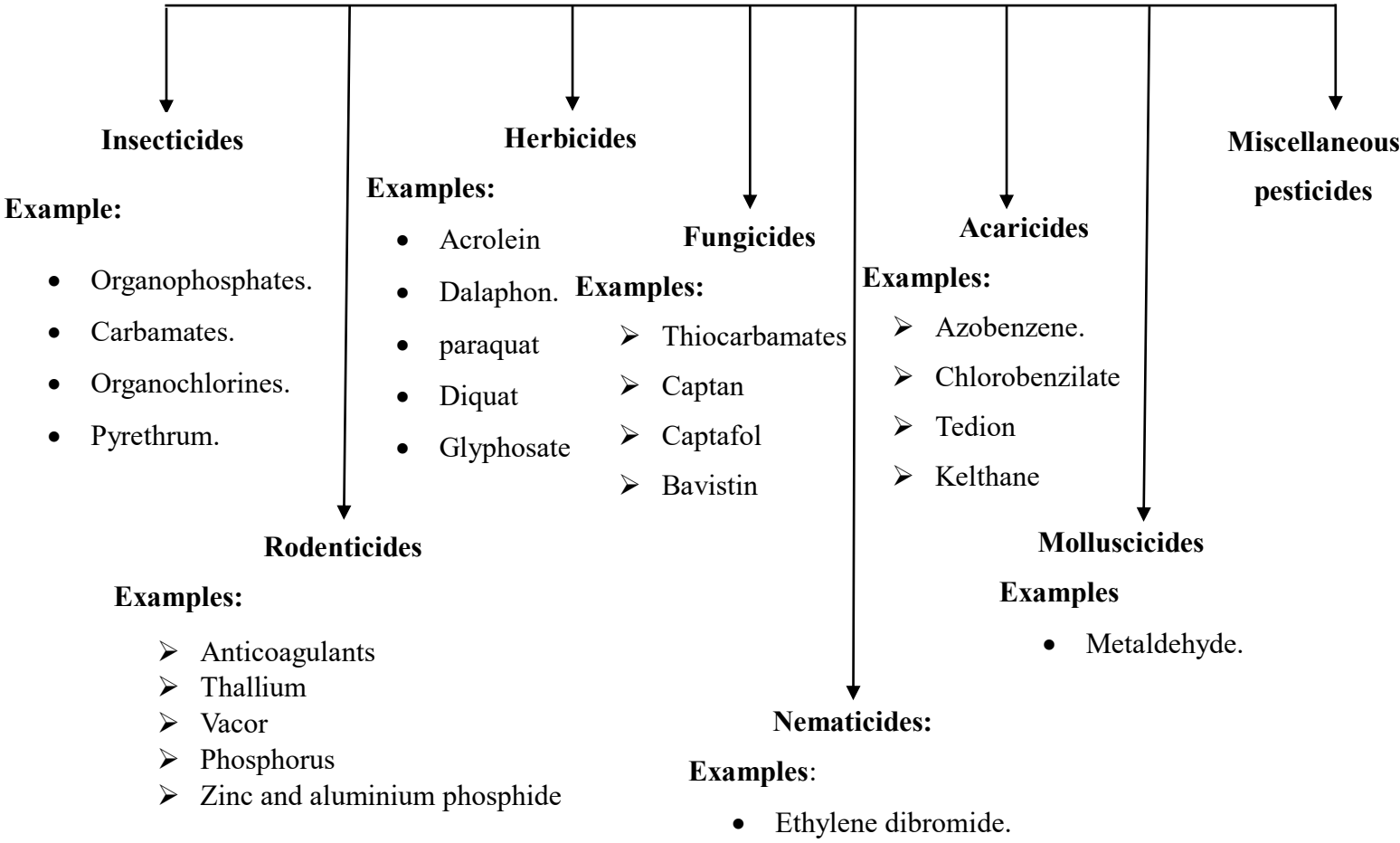
Keywords: Pesticides, organochlorines,carbamates, pyrithrins, mechanism, toxicokinetics , diagnosis, symptomatic treatment.

INTRODUCTION OF PESTICIDES: [1.VV. Pillay et al 2013]

Definition of Pesticides:

Pesticides are compounds that are used to kill pests which may Be insects, rodents, fungi, nematodes, mites, ticks, molluscs, and unwanted weeds or herbs.

CLASSIFICATION OF PESTICIDES: [2. Octiara DL et al 2018]



Introduction of chlorine pesticide: [3. Singh Z, Kaur et al 2016]

Pesticides are mainly applied in the farming industry to control vectors that reduce the quantity and quality of farm produce.

- The pesticides are sprayed directly on the crops then farmers inhale those pesticides and metabolized in the human body .it have been linked to a wide variety of health effects, ranging from acute to chronic toxicity; such as cancer, endocrine disruption, and neurological effects.

- It is in literature that while every country has its own regulations and laws regarding pesticides, governments in developing countries do not adequately address the unsafe use of pesticides.
- In this regard, health risk assessment studies have focused on the permitted less-persistent pesticide products especially organophosphorus, carbamates, nicotinoid, and pyrethrins .
- The natural effect of the use of pesticides is identified with the elemental properties that are significant for his or her viability as a pesticide. Pesticides are harmful Enough to influence all scientific classifications of biota, Including non-target life forms.
- Many pesticides Are resistant to environmental degradation so they can Withstand in the treated areas, but these properties Also have a long-term effect on natural ecosystem but these properties Also have a long-term effect on natural ecosystem.
- It has been found in seal and penguin Networks in Antarctica, and in fish around coral reefs and remote oceans.
- It Was banned in many countries since 1980.

Organochlorine: [4. DEZIEL N ET AL2020]

- Organochlorines show a colossal combination of Structures with much different engineered properties Because of high atomic heap of chlorine.
- It is been seen that Assimilation of organochlorine through skin and gut and found more in human fat tissues.
- Organochlorine has been banned in the United States And other nations due to its carcinogenicity and toxicity.
- In several regions monitoring blood cholinesterase from 347 workers in Agriculture in Central Java, it had been found that 23.64% Of workers were moderately poisoned and 35.73% were Very poisonous. Nearly all chronic diseases suffered by Farmers were caused by the utilization of pesticide sprays That were released into the air, which, if inhaled through the nose and thru the mouth, can enter the lungs and Damage them, and quickly the pesticide enters the blood and spreads toxins. Throughout the body.

Classification of organochlorines: [5. Kurniadi D et al 2018]

Organochlorine insecticides are classified into three subgroups:

1. Dichlorodiphenylethanes:

Examples: Dicofol, methoxychlor and perthane.

2. Chlorinated cyclodienes:

Examples: Aldrin, dieldrin, endrin, chlordane, endosulfan, and heptachlor.

3. Hexachlorocyclohexanes(g):

Examples:BHC, chlordane, lindane, mirex, and toxaphene.

Physical Appearance: [6.Die Q et al 2015]

These compounds are available as dusting powders, wettable Powders, emulsions, granules and solutions.

Usual Fatal Dose:

- DDT, lindane: 15 to 30 grams.
- Aldrin, dieldrin, endrin: 2 to 6 grams. Toxicity Rating: Dieldrin is placed in the "extremely toxic" Category (LD50: 1 to 50 mg/kg), while DDT, endosulfan, and Lindane are considered "highly toxic" (LD50: 51 to 500 mg/kg), As per the Insecticide Rules, 1971. In addition, the following are extremely toxic: endrin, Aldrin, chlordane, and toxaphene, while these are highly toxic: Kepone, heptachlor, mirex. The following are least toxic: Methoxychlor, perthane, kelthane, chlorobenzilate and hexa Chlorobenzene. Acute hazard potential may be ranked (highest to lowest) Approximately as: endrin, aldrin, dieldrin, chlordane, toxa-Phene, kepone, heptachlor, DDT and methoxychlor.

Toxicokinetics: [7. Purnama SG.et al 2017]

Commercial preparations of organochlorines are commonly Dissolved in petroleum distillates which form emulsions when added to water.

- All the organochlorines can be absorbed trans dermally, orally, and by inhalation.
- Gastrointestinal absorption of these agents is generally efficient, particularly in the presence of absorbable lipid (animal or vegetable) fat.
- DDT is the Least well absorbed trans dermally, while dieldrin is very well Absorbed. Many of these compounds are metabolized slowly and persist in tissues (especially fat) for prolonged periods.
- High residue levels from organochlorine insecticide poisonings Are found in adipose tissue. However, unlike other organochlorine pesticides, methoxychlor does not substantially accumulate in fatty tissues of humans.
- Excretion of organochlorine compounds does not follow First order kinetics. As body stores get lower, the half-life for the remaining store increases dramatically.
- This is probably Due to complex lipoprotein binding; wherein different bound Forms exhibit different dissociation characteristics.
- It is still Possible to classify the organochlorines roughly in terms of the rapidity of excretion from storage levels that represent an Acute toxic threat.

Excreted or metabolized within hours to a few days: [8. Prananditya R et al 2016]

Chlordane (except the heptachlor component)

- Chlorobenzilate
- Endosulfan
- Endrin
- Kelthane
- Methoxychlor
- Perthane
- Toxaphene.

Excreted within several weeks to a few months:

- Aldrin
- Dieldrin
- Heptachlor
- hexachlorobenzene.

Excreted only over several months or years:

- Beta isomer of benzene hexachloride
- DDT
- Kepone
- Mirex.

Mode of Action: [9. Mahacitra RA et al 2014]

Organochlorines do not depress cholinesterase enzymes. These Compounds act by various other mechanisms.

- DDT and analogues affect the sodium channel and sodium Conductance across the neuronal membrane especially of the axon. They also alter the metabolism of serotonin, Noradrenaline and acetylcholine.
- The cyclodienes and lindane appear to inhibit the GABA-Mediated chloride channels in the CNS.
- The neurotoxic mechanism of endosulfan involves inhibition of the calmodilin dependent Ca2+ -ATPase activity, Alterations in the serotoninergic system, and inhibition of GABA receptors.
- An important property of the chlorinated hydrocarbons, particularly toxaphene, chlordane, DDT, and lindane is their capacity to induce the drug-metabolizing enzymes of the Liver. Most of these agents cause liver necrosis and they are Potent enzyme inducers. Evidence suggests an important role of benzoquinones in the hepatotoxicity of chlorinated hydrocarbons as opposed to traditional epoxides. Cytochrome P450 appears to be associated with covalent protein binding of reactive metabolites.

Symptoms: [10. Putri AC, et al 2016]

Acute Poisoning:

- GIT: nausea, vomiting, abdominal pain, hyper aesthesia or paraesthesia of the mouth and face.
- CNS: headache, vertigo, myoclonus, tremor, ataxia, nervousness, amnesia, rapid and dysrhythmic eye Movements, mydriasis, weakness, agitation, confusion, And convulsions. Occasional reports have associated Peripheral neuropathy with exposure to organochlorine.
- Other systems: fever, aspiration pneumonitis, renal Failure. Coronary spasm, hypotension, and sinus Tachycardia may occur following exposure. Dieldrin, Endrin, chlordane, toxaphene, and DDT are direct Respiratory depressants. Severe metabolic acidosis has been reported.
- Organochlorine pesticides such as DDT pass through the placenta, with an average level in the newborn blood reaching around a third of that in maternal blood. They can also be found in breast milk.

Chronic Poisoning: **[11. Suryono CA,et al 2016]**

- Long-term exposure to some of these compounds (chlordecone, chlordane, heptachlor) results in cumulative toxicity with manifestations such as weight loss, tremor, weak-Ness, opsoclonus, ataxia,

pseudotumor cerebri, abnormal mental changes, oligospermia, and increased tendency to Leukemias, thrombocytopenic purpura, aplastic anemia, Hepatomegaly centrilobular hepatic necrosis and liver cancer. The International Agency for Research on Cancer (IARC) Has listed some of these agents (e.g., DDT) as "possibly carcinogenic to humans", although it also categories them as being Inadequately assessed for human carcinogenic potential. For Other agents (e.g., aldrin), carcinogenicity has been demon-Started in animal studies, but insufficient data has accrued from human studies.

Diagnosis: [12. Shoiful A et al 2015]

- Abdominal radiograph may reveal the presence of certain Organochlorines which are radiopaque.
- Organochlorines can be detected in serum, adipose tissue, And urine by gas chromatography.
- Blood chlorinated hydrocarbon levels are not clinically useful following acute exposure. For most compounds they reflect cumulative exposure over a period of months or years rather than recent exposure.
- Measurement of organic halogen compounds in urine is suggested as an indicator of exposure. Sensitivity is as low as 1 mcg of organic halogen per 100 ml of urine.

Experts classify the effects of toxicity by the length of exposure:

- Acute effects occur within minutes to 24 hours.
- Subacute effects appear 24 hours to 2 weeks after exposure.
- Chronic effects appear from weeks to several years after exposure.

Treatment for organochlorine poison: [13. Islam R,et al 2018]

1.Decontamination-The same measures as detailed under organophosphate poisoning must be undertaken.

- Move patient from the toxic environment to fresh air.
- Monitor for respiratory distress. If cough or difficulty.
- In breathing develops, evaluate for hypoxia, respiratory Tract irritation, bronchitis, or pneumonitis. Administer 100% humidified supplemental oxygen, perform Endotracheal intubation and provide assisted ventilation as required. Administer inhaled beta-adrenergic agonists If bronchospasm develops.
- Exposed skin and eyes should be flushed with copious Amounts of water. Remove contaminated clothing and Jewelry; wash skin, hair and nails vigorously with Repeated soap washings. Leather absorbs pesticides; All contaminated leather should be discarded. Rescue Personnel and bystanders should avoid direct contact with contaminated skin, clothing, or other objects. [14. Anand N et al 2020]

2.Do not give oils by mouth. They tend to increase intestinal absorption of these lipophilic toxicants.

3.Seizures should be controlled with benzodiazepines, Phenytoin, or phenobarbitone in the usual way. If they are Not effective enough, sodium thiopentone can be administered IV, or neuromuscular blockade is done.

4.Monitor for respiratory depression, hypotension, arrhythmias, and the need for endotracheal intubation. Evaluate for Hypoxia, electrolyte disturbances, and hypoglycemia (if Present, treat with intravenous dextrose: 50 ml IV (adult), Or 2 ml/kg (child) of 25% dextrose). [15. Barletta M,et al 2019]

5.Cholestyramine, a non-absorbable bile acid binding anion Exchange resin is effective in enhancing the faecal excretion of organochlorine compounds, particularly chlordecone. It Is administered at a dose of 16 gm/day for several days. It Can be mixed with fruit juice and given orally (4 gm, 6thHourly). It can interfere with absorption of other therapeutic Drugs which must therefore be administered either 1 hour Before, or 4 hours after each dose of cholestyramine.[16]

6.Hyperthermia should be managed aggressively with Cooling. [17. Nuapia Y et al 2016]

7.Supportive measures-special attention must be paid to the Airway and breathing, and adequate circulation should be Maintained. [18. Wetland Park et al 2018]

8.The following are contraindicated-oil-based cathartics, Adrenaline, and atropine. Do NOT administer adrenergic Amines, which further increase myocardial irritability and produce refractory ventricular arrhythmias.

9.Haemodialysis and hemoperfusion have not been proven Effective.[19]

Carbamates: [20. Martínez-López E,et al 2015][21.Mouly TA et al 2016]

Definition:

A salt or ester containing the anion NH_2COO-or the group -$OOCNH_2$, derived from hypothetical compound carbamic acid [ethyl carbamate].

Classification: **[22. Annida S et al 2017]**

The carbamate insecticides are of two types, esters of N-methyl (or N,N-dimethyl) carbamic acid with either a phenol or an oxime. Carbaryl and pirimicarb are examples of the phenolic type. Aldicarb and methomyl are examples of the oxime type.

Physical appearance: [23. Mahyuni EL et al 2015]

According To physical features carbamates are colorless crystalline Substances or liquids. They Dissolve weakly in water but Dissolve well in organic solvents, and after absorption Into the Body, they undergo rapid biotransformation. [24. Maulidiniawati N,et al 2016]

Toxicokinetics: [25. Syakir MA, et al 2018]

Carbamates are rapidly metabolized. They are rapidly Hydrolysed by liver enzymes to methyl Carbamic acid and a variety of low toxicity phenolic substances **[26. Pirard C et al** 2018**].** These metabolites May Sometimes be measured in urine as long as 2 to 3 days.

Fatal dose: [27. Alharbi OML et al 2018]

The following are extremely toxic (LD50: 1 to 50 mg/kg), Or highly toxic (LD50: 51 to 500Mg/kg)—Aminocarb, Bendiocarb, Benfuracarb, Carbaryl, Carbofuran, Dimetan, Dimetilan, Dioxacarb, Formetanate, Methiocarb, Methomyl, Oxamyl, Propoxur.The following are Moderately toxic (LD50: 501 to 5000 Mg/kg), or slightly toxic

(LD50: more than 5000 mg/kg)-Aldicarb**,** Bufencarb, Isoprocarb, MPMC, MTMC,Pirimicarb. **[28. Shapiro GD et al 2016]**

Mechanism of action: [29. Rahman ML,et al 2019]

Carbamate insecticides enter the body through the skin, digestive and respiratory tracts. They are metabolized quite quickly and excreted in the urine. The mechanism of action of toxic carbamates is similar to the mechanism of action of organophosphorus compounds (Ops, Which Involves blocking the activity of cholinesterase by binding to it **[**30.. Madrigal JM,et al 2004]. Most authors believe that the Observed symptoms of poisoning indicate the existence of yet other, unexplained mechanisms of toxic action of this group of compounds. [31. Harahap FS et al 2018]

Clinical symptoms: [32. Mukadar LA et al 2018]

Miosis, a muscarinic effect, is characteristic of severe and moderately severe poisonings, but may appear late. Pupil dilation may occur as a nicotinic effect and may be present in up to 10% of patients.

- Chest tightness
- Bronchospasm increased pulmonary secretions; rales may develop secondary to Muscarinic effects.
- Acute lung injury (pulmonary oedema)
- Headache
- Convulsions
- Dizziness
- Blurred vision [33. Ahmadi LS et al 2020]
- Tremor
- Paresis
- Mental depression,
- Coma,
- Delayed neuropathies, various [34. Purwandari R,et al 2017]
- Dystonias,
- Weakness,
- Muscle twitching, and convulsions [35. Ipmawati PA, Setiani O, et al 2016]

Diagnosis: **[36. Putri MS et al 2016]**

Measurement of cholinesterase activity in blood chest x-ray one technique for assessing absorption of the principal n-methyl carbamate compounds is measurement of specific phenolic metabolites in urine, e.g., Carbaryl (alpha-naphthol), carbofuran (carbofuran phenol) propoxur (isopropoxyphenol). [37. Istianah, et al 2018]

Treatment: **[38. Rasiska S, et al 2017]**

In carbaryl poisoning, oxime therapy, can lead to the production of a carbamylated oxime which may be a more potent acetylcholinesterase inhibitor than carbaryl itself In all cases, administer Atropine in repeated doses intravenously until atropinisation is achieved (indicated by drying of Pulmonary secretions) [39. Valenzuela A,et al 2016]. Adult dose-2 to 4 mg IV every 10 to15 minutes. Pediatric dose—0.05 Mg/kg IV every 10 to 15 Minutes convulsions can be controlled with a benzodiazepine (diazepam or lorazepam). If they persist or recur, administer. [40. Puspa SM et al 2017]

Pyrithrins:

Definition of pyrithrins: [41. Jayaraj.et al 2016] [42.Hu, W et al 2010]

Pyrethrins are pesticides found naturally in some chrysanthemum flowers. They are a mixture of six chemicals that are toxic to insects. Pyrethrins are commonly used to control mosquitoes, fleas, flies, moths, ants, and many other pests. Pyrethrins are generally separated from the flowers.

Classification of pyrithrins: [43. Rallis, G.N.et al 2012]

Pyrithrins are divided into two groups according to their chemical structures:

- Type I pyrithrins are devoid of a cyano moiety at the alpha-position (i.e. permethrin, PERM) [44. Yahaya, A. et al 2017]
- While type II pyrithrins have an alpha-cyano moiety (i.e., cypermethrin, CY). [45.Sun, H et al 2016]

Clinical uses: [46.Karami-Mohajeri S, et al 2017]

- These compounds are used as household insect repellants and insecticides. They are sold as liquids, sprays, dusts, powders, mats, and coils.
- They are also used to prevent pest infestation in granaries, and in agriculture as pesticides. [47. Kim S et al 2019]
- Pyrethrum extract is effective for treating pediculosis of the head, body and pubic area These compounds are used as household insect repellants and insecticides. They are sold as liquids, sprays, dusts, Powders, mats, and coils. [48. National Center for Biotechnology Information 2020]
- They are also used to prevent pest infestation in granaries, And in agriculture as pesticides.
- Pyrethrum extract is effective for treating pediculosis of the head, body and pubic area. [49 . Reddy DS et al 2016]

Toxicokinetics: [50. Wille T,et al 2013]

- Pyrithrins are rapid absorbed through GIT.
- Liver enzymes metabolizes the pyrithrins.
- This pyrithrins can only enter through the inhalation & ingestion.

Physical appearance: **[51. Bajracharya SR, et al 2016]**

- Liquids (spraying)

Usual fatal dose: [52. Jokanović M et al 2018]

- Pyrethrum has an LD50 of over 1 gm/kg. However, the minimal lethal dose of pyrethrum is not clearly established, though it is probably in the range of 10 to 100 grams. Most cases of toxicity are actually the result of allergic reaction.

Mechanism of action: [53. King AM,et al 2014]

Structurally, pyrethroids are of 2 types-

- Type I pyrethroids do not contain a cyano group, e.g., Permethrin.
- Type II pyrethroids contain a cyano group, valley e.g., deltamethrin, cypermethrin, fenpropathrin, fenvalerate, etc. Like DDT, pyrethroids prolong the inactivation of theSodium channel by binding to it in the open state.
- Type II Agents are more potent in this regard, and also act by inhibiting GABA-mediated inhibitory chloride channels.
- Low toxicity in mammals is probably due to rapid metabolic breakdown in the Liver: pyrethrum is broken down mainly by oxidation of the Isobutenyl side chain of the acid moiety and of the unsaturated Side chain of the alcohol moiety with ester hydrolysis playing a role.
- Some organophosphates may enhance pyrethrin toxicity due to competition for carboxyesterases responsible for rapid detoxification of pyrethrins via ester hydrolysis. Very young children are perhaps.
- Most susceptible to poisoning by pyrethroids because they may not hydrolyse the pyrethrum esters efficiently. Two types of allergens present in crude pyrethrum oleoresin Have been identified: glycoproteins or glycopeptides ranging In molecular weight from 60,000 to 200,000 (most important) And the sesquiterpene lactones, principally pyrethrosin (minor importance). Refined pyrethrins and synthetic pyrethroids are Said to have little or no allergenic effect.

Diagnosis:

1. Serum cholinesterase levels are normal.
2. ECG may demonstrate ST-T changes, sinus tachycardia, And ventricular premature beats.
3. A color test with 2-2 (2-aminoethylamine) ethanol produces red to violet color in the presence of pyrethroidal substances. It is however not suitable for analysis of pyrethrins in body fluids, except, possibly at very high concentrations.

Treatment of pyrithrins: [54. Naughton SX,et al 2018]

Skin contact-Decontaminate with soap and water.

1. Eye contact-Irrigate with normal saline or water for 10 to 15 minutes.
2. Systemic poisoning-Mild to moderate allergic reactions may be treated with Antihistamines (e.g. Diphenhydramine 50 mg orally, Intravenously, or intramuscularly initially, then 25 to 50 Mg orally every 4 to 6 hours for 24 to 72 hours) with Or without inhaled beta agonists, corticosteroids (e.g. Methyl prednisolone 1 to 2 mg/kg intravenously every 6 to 8 hours) or adrenaline (1:10,000 solution, 3 to 5 Ml diluted in 10 ml 0.9% saline slow intravenous push Over 5 to 10 minutes).

a) Treatment of severe anaphylaxis Also includes oxygen supplementation, aggressive Airway management, adrenaline, ECG monitoring and IV fluids.

b) In massive ingestions, stomach wash can be done after making sure that there are no petroleum distillate additives.

c) Activated charcoal is beneficial. However, if the pyrethrin is formulated in an organic solvent, activated charcoal is unlikely to be of benefit. If the pyrethrin is formulated in a petroleum base, the risk of hydrocarbon pneumonitis may exceed the toxic hazard of the insecticide. Gastric decontamination is therefore, generally not recommended.

d) Oils and fats (including milk) promote the intestinal absorption of pyrethroids and should be avoided.

e) Oxygen and ventilatory assistance must be administered as indicated.

f) Bronchospasm is treated with standard bronchodilators. Administer beta2 Adrenergic agonists. Consider use Of inhaled ipratropium and systemic corticosteroids. Monitor peak expiratory flow rate, monitor for hypoxia And respiratory failure, and administer oxygen as necessary. Consider systemic corticosteroids in patients with Significant bronchospasm, e.g., prednisone 60 mg/day (adult), or 1 to 2 mg/kg/day (child).

g) Seizures can be controlled with diazepam. Consider phenobarbitone if seizures recur after diazepam 30 mg (adults) or 10 mg (children > 5 years).

h) If hypotensive give 500 to 2000 ml crystalloid initially (20 ml/kg in children) and titrate to desired effect (stabilization of vital signs, mentation, urine output); Adults may require up to 6 to 10 liters/24 hours. Central Venous or pulmonary artery pressure monitoring is Recommended in patients with persistent hypotension. Vasopressors such as dopamine should be used in refractory cases unresponsive to repeated doses of Adrenaline, and after vigorous intravenous crystalloid Rehydration.

i) Atropine and oximes are contraindicated, but some Investigators recommend the former for drying up Secretions.

j) Cutaneous paraesthesias are said to respond to topical applications of vitamin E.

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Conclusion:

In this article we represented about organochlorines, carbamates, and pyrethrin poisoning. Nowadays the farmers due to these are more available to them .They consuming these pesticides for suicides in a condition of economical burden. These produce fatal effects. The treated individual cannot lead their life effectively as before. The treatment for these pesticides such as symptomatic management in organochlorines and pyrithrins. In carbamates antidote administration (oximes) takes place.

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