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Pyrethrins Toxicity Threatened the Life without Immediate Emergency Medical Management

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ABSTRACT:- Pyrethroids are common household insecticides. Even though they are less toxic to humans, reports of accidental and suicidal poisoning are not uncommon. Pyrethroids poisoning may threaten the human life if there are no immediate and emergency medical management, where as there are many fatalities reported due to pyrethroids poisoning especially for the suicidal attempt. The most serious effect of the pyrethroids toxins in humans are seizures, coma, cardiac arrhythmias, and GIT bleeding. We report a 3 case of suicidal attempt by pyrethrins toxin. The neurotoxicity was the most signs and symptoms predominantly appearing on the three cases. The mechanism of pyrethroids neurotoxicity is believed to be due to its ability to modify sodium, chloride, and calcium channels of the neurons, and the inhibitory effect on the action potential of the cells. Our message in this paper pyrethroids are dangerous compounds, the poisoning with this material need urgent medical interventions, the long term effects of pyrethroids need further studies and follow up.

Keyword:- Pyrethrins, pyrethroids poisoning, Chrysanthemum, organ phosphorus.

I. INTRODUCTION

The pyrethrins are class of organic compounds normally derived from Chrysanthemum Cinerariifolium that have potent insecticidal activity by targeting the nervous system of insects. Pyrethrin naturally occurs in chrysanthemum flowers, thus is often considered an organic insecticide, or at least when it is not combined with piperonyl butoxide or other synthetic adjuvants. Their insecticidal and insect-repellent properties have been known and used for thousands of years (1, 2,3,4,5,6). Pyrethrins are gradually replacing organophosphates and organochlorides as the pesticides of choice, since these other compounds have been shown to have significant and persistent toxic effects to humans. Because they are biodegradable compounds, pyrethrins are now widely regarded as being preferable to pyrethroids, which is the name of a group of synthetic analogues of pyrethrin that accumulate in the environment.

Pyrethrum was first recognized as having insecticidal properties around 1800 in Asia and was used to kill ticks and various insects such as fleas and mosquitos. Six individual chemicals have active insecticidal properties in the pyrethrum extract, and these compounds are called pyrethrins. Pyrethrum looks like a tan-colored dust as ground flowers or a syrupy liquid as the crude extract. Pyrethrins are only slightly soluble in water, but they dissolve in organic solvents like alcohol, chlorinated hydrocarbons, and kerosene.

Pyrethroids are manufactured chemicals that are very similar in structure to the pyrethrins, but are often more toxic to insects, as well as to mammals, and last longer in the environment than pyrethrins. More than 1000 synthetic pyrethroids have been developed, but less than a dozen of them are currently used in the United State. Pyrethrins and pyrethroids are often combined commercially with other chemicals called synergists, which enhance the insecticidal activity of the pyrethrins and pyrethroids. The synergists prevent some enzymes from breaking down the pyrethrins and pyrethroids, thus increasing their toxicity. (7)

Well after their use as insecticides began, their chemical structures were determined by Hermann Staudinger and Lavoslva Ruzicka in 1924. (9w). pyrethrin1 (C11H28O3) and pyrethrinii (C11H28O5) are structurally related to esters with a cyclopropane core. Pyrethrin i is a derivative of (+)-trans-chrysanthemic acid (10,11 w). pyrethrin ii is closed related, but one methyl group is oxidized to a carboxymethyl group, the resulting core being called pyrethric acid. Knowledge of their structures opened the way for the production of synthetic analogues, which are called pyrethroids. Pyrethrins are classified as terpenoids. The key step in the biosynthesis of the naturally occurring pyrethrins involves two molecules of dimethylallyl pyrophosphate, which jointo form a cyclopropane ring by the action of the enzyme chrysanthemyl diphosphate synthase. (8).

Pyrethroids are some 2250 times more toxic to insects than mammals because insects have increased sodium channel sensitivity, smaller body size and lower body temperature. In addition, mammals are protected by poor dermal absorption and rapid metabolism to non-toxic metabolites Pyrethroids are ion channel toxins that interfere with the function of the nervous system. They modify the "gating" characteristic of neuronal voltage-sensitive sodium channel to delay their closure, thereby prolonging neuronal excitation (9).

The toxic effects of pyrethroids result from this neuronal excitation and include a wide spectrum of signs and symptoms from paresthesia and increased salivation, through to seizures and potentially death. Allergic reactions, including contact dermatitis or asthma, are only rarely reported with synthetic pyrethroids (10).

Cutaneous toxicity as a case of skin necrosis caused by the use of prallethrin (mosquito repellent) as a type of pyrethroids registered by Botnariu G et el, which is rarely happened in comparing to the welldocumented pyrethroid poisoning involving the gastrointestinal, respiratory, cardiac, and nervous systems. (11) Reports of respiratory symptoms and allergic reactions caused by inhalation of pyrethroids of three cases reported in Japan in spite of the level of exposure were low in all three cases compared to oral lethal dosage, these cases presented with serious respiratory symptoms (12). A complete heart block reported in a case of 59 years old female who presented with syncope after an accidental exposure to bed bug repellant spray at home (where the pyrethroids are the major components of that spray) (13). In this paper we are reported three cases of suicidal attempt by the pyrethrin compound as an home used insecticide. The three patients were admitted to the emergency department in different times from 15th of September 2017, 28th of June 2018, and 11th of September 2018 in AlSadiq general teaching hospital, Hilla, Babylon, Iraq. The three cases reported and follow up from the time of the admission to the time of discharging.

CASE 1: A 33 years old male private worker, with stressful life events, presented to the emergency (ED) with suicidal attempt, by ingestion of tetramet hrin poisonous material. On arrival patient was comatose with recurrent tonic-clonic fit, pinpoint pupils; not react to light, there was rhinorrhea, frothy secretion, with muscular fasciculation. On examination the GSC (Glasgow coma scale) was 3/15, pulse rate(PR) 50-60 beats/ minute, blood pressure(BP) 80/50 mmHg, respiratory rate(RR) 23/ minute. The chest exam revealed bilateral coarse crepitation. Then the patient referred for respiratory care unit(RCU), endotracheal tube(ETT) done with mechanical ventilation and midazolam infusion given till the control of fit. The patient receives atropine 1 ml/15 minute for 10 doses, antibiotic prophylaxis, intravenous fluid(IVF) 2500ml/24 hours.

The patient developed melena and hematemesis; kept on PPI (proton pump inhibitor) infusion with follow up. Then patient samples send for toxicological screen which revealed no organophosphorus or other known toxins. The patient gradually develops good motor response, eye opening, response to verbal stimuli, the patient weaned from ventilator, removal of ETT after about 24 hours from admission. The patient discharge after 48 hours with outpatient follow up till 30 days revealed that the patient complains of headache, light headedness, amnesia with acral paresthesia; all these resolved after one month with complete recovery.

CASE 2: 19 years old male patient fail during his secondary school graduation, he had suicidal attempt by adding insecticide sprayed its content into a cup of water and drink it. The insecticide was in form of permethrin. The patient arrived to ED with recurrent tonic clonic fit, muscular fasciculation, pin point pupil not react to light, rhinorrhea, frothy secretion from the mouth, the chest full of coarse crepitation, SPO2 was 70% with high concentration, continuous O2 delivery through an O2 mask. PR was 55 beats/minute; BP was 90/40 mmHg. There was a loss of sphincter control, the GCS was 3/15. The patient admitted to the RCU, with ETT and mechanical ventilation, with PEEP 5-10 cm H2O with midazolam infusion till the seizure controlled. The patient kept on IVF, antibiotic prophylaxis, regular suction of secretion and physiotherapy to the chest.

Atropine 1 mg/ 15 minute for 20 doses to decrease the secretion. There was normal serum electrolyte, RBS, BUN, SCr, CBC, CXR, the ECG revealed bradycardia, the CT scan of the brain was negative. Toxicological screen revealed negative for known poisonous material and toxin On follow up the patient recover normal motor, eyes response within 18 hours, the patient weaned from mechanical ventilator with removal of EET. Then the patient kept in the ward and discharged 48 hours from the time of first arrival. CASE 3: 28 years old male patient farmer with suicidal attempt by ingestion of pyrethrin derivative admitted to ED then to the RCU with coma, continuous fit, upper GIT bleeding, rhinorrhea, frothy secretion from the mouth, chest full coarse crepitation, muscular fasciculation, pin point pupil not response to light, and there was lacrimation, PR 50/minute, BP 90/60 mmHg, soft abdomen, the GCS was 3/15. The patient kept on mechanical ventilation and ETT, midazolam infusion for seizure control, IVF, antibiotic prophylaxis, PPI.

The patient awakes within 24 hours and try to bite and cut his ETT, then the patient weaned from the ventilation and removal of the ETT done, kept for another 24 hours in the ward and discharged then. The CT brain, CXR, ECG, CBC, RBS, RFT, S electrolyte, was negative. Toxicological screening report revealed no known toxic material.

II. DISCUSSION

The effects of pyrethroids are on sodium and chloride channels. Pyrethroids modify the gating characteristics of voltage-sensitive sodium channels to delay their closure. A protracted sodium influx (referred to as sodium "tail current") ensues which, if it is sufficiently large and/or long, lowers the action potential threshold and causes repetitive firing; this may be the mechanism causing paresthesia. At high pyrethroid concentrations, the sodium tail current may be sufficiently great to prevent further action potential generation and 'conduction block ensues'. Only low pyrethroid concentrations are necessary to modify neuron function. Type II pyrethroids also decrease chloride currents through voltage-dependent chloride channels and this action probably contributes the most to the features of poisoning with type II pyrethroids. At relatively high concentrations, pyrethroids can also act on GABA-gated chloride channels, which may be responsible for the seizures seen with severe type II poisoning.

Despite their extensive world-wide use, there are relatively few reports of human Pyrethroid poisoning. Pyrethroid ingestion gives rise within minutes to a sore throat, nausea, vomiting, and abdominal pain. There may be mouth ulceration, increased secretions and/or dysphagia. Systemic effects occur 4-48 hours after exposure. Dizziness, headache and fatigue are common, and palpitation, chest tightness and blurred vision less frequent. Coma and convulsions are the principle life-threatening features. In a study of 573 cases of Pyrethroid poisoning there was seven fatalities among them. And there was one fatality in another study of 48 cases of Pyrethroid poisoning (9).

The possibility that the pyrethroids induce hypersensitivity, which may be fatal when the respiratory tract is involved, has been debated for many years. A few clinical reports this suggestion but the limited epidemiological evidence available against it. The number of reports of toxicity caused by pyrethrins has greatly decreased over recent years.

The pyrethrins are generally of low acute toxicity but convulsions may occur if substantial amounts are ingested. Two deaths from acute asthma have been attributed to pyrethrins and clinical reports suggest that they may also cause a variety of forms of dermatitis, while ocular exposure has resulted in corneal erosions (14).

Although clinical features resulting from acute accidental exposure to pyrethroids are well described (e.g. paresthesia, and respiratory, eye and skin irritation), information regarding their chronic effects at low concentrations is both limited and controversial. Several recent epidemiological studies have raised concerns about potentially adverse effects on sperm quality and sperm DNA, reproductive hormones, and pregnancy outcomes. Early neurobehavioral development after in utero exposure is discussed. Further research is needed to clarify the possible risks associated with long-term environmental exposure to pyrethroids (15)

Patients with significant Pyrethroid ingestion can present with severe symptoms and signs which could constitute a medical emergency, and should immediately referred to hospital for life support measures and ongoing monitoring (11). Yang et al (17) analyzed the clinical features of

48 patients (38 intentional and 10 accidental) with poisoning due to insecticide formulations containing permethrin, xylene, and surfactant. In their observation, gastrointestinal symptoms and signs were most common (73%), which include sore throat, mouth ulceration, dysphagia, epigastric pain, vomiting and melena. Central nervous system involvement was present in 33% which include confusion, seizures, and coma. Pulmonary involvement in the form of aspiration pneumonia and pulmonary edema were present in 29% of the patients. Mild renal dysfunction (10%) and hepatic dysfunction (6%) were also observed. Arrhythmias were observed in 4% (two cases) but the study has not explained the nature of the observed arrhythmias.

Our data (look at the table) revealed there was no significant serum electrolytes changes during the state of pyrethrin poisoning but there were many conditions may threatened the life of the patients without medical interference ; the severe convulsion and coma, the low oxygen saturation of the blood, the frothy secretion of the mouth with coma and convulsion may lead to serious aspiration pneumonia which may threaten the life of the patients, and the other symptoms accompanying the state of the poisoning, for this reason the immediate medical interventions at the time of the pyrethroids compounds poisoning is a mandatory subject whatever the pyrethroids compound are metabolized by the liver and very little amount staying blood-circulating, the immediate emergency medical management is the cornerstone of the overcoming threatening the life of patients with the pyrethroids poisoning.

The initial presentation of the cases presenting in this study are similar to organophosphorus, there were the odor and the color similar as the organophosphorus and the initial diagnosis in emergency department was organophosphorus toxicity. the starting management was as a cases of organophosphorus but the searching was negative for organophosphorus; for this reason we should put in mind the history of the case is very important beside the investigation, the toxicological investigations and the clinical presentations in order to manage the patients in an ideal management. Increased incidences of liver and thyroid tumors observed in rats treated with pyrethrins are threshold phenomena of negligible relevance to low doses to which humans are exposed. Studies performed to investigate the mechanism by which pyrethrins cause tumorigenesis in the liver and thyroid, and also suggested that a test for gene mutation in mammalian cells and more detailed information

on case reports of adverse health effects in humans, for which only an abstract was available, should be submitted for evaluation (16).

The long-term effect of the pyrethroids compound on the health and their pathological effect on the human being not get its satisfactory effort and there is a little data, for these reason the follow up of the pyrethroids poisonous should be following for at least 2 years from the time of the poisoning.

Our aim in this study is to arouse attention to a new household agent, started to increase as an incriminated agent in suicide attempt, other point that the odor and the colors used in the preparation of pyrethrin same as that in organophosphorus.

The last point, that all cases presented to emergency department with suicide attempt, having pin-point pupils, frothy secretions, chest fully of crepitation and recurrent seizures, all the same as in organophosphorus, so all cases has been treated as organophosphorus with atropine and if present obidoxime as antidote for organophosphorus till the result of toxicology screen appeared or Empty container for the offending poison (if available) had been inspected which revealed that the cause is not organophosphorus. Providing that pyrethrin derivatives had substituted organophosphorus as pesticides, insecticides, or mosquito repellents, for these reasons careful inquiry must be taken for the poisonous material or agent at all times in suicide attempts.

Table of investigation done to the patients:

investigation	Case 1	Case 2	Case 3
WBC	9,3*10^3	10,5*10^3	7.8*10^3
Platelet	232*10^3	350*10^3	250*10^3
PCV	44	43	46
S K +	3.8 mg/dl	4.2 mg/dl	4.3 mg/dl
S Ca+2	2.3 mg/dl	2.2 mg/dl	2.2 mg/dl
S Cl -	105 mg/dl	100 mg/dl	101 mg/dl
S Na+	145 mg/dl	135 mg/dl	142 mg/dl
SHCO$_3$	23 mg/dl	20 mg/dl	25 mg/dl
RBS	7.2 mmol/dl	8.3 mmol/dl	6.6 mmol/dl
BUN	5 mmol/dl	6.2 mmol/dl	7.1 mmol/dl
SCr	103 umol/dl	95 umol/dl	110 umol/dl
SGOT	31	33	35
SGPT	32	20	38
S alk. Phosp.	90	72	78
TS Protein	8.1 g/l	8.9 g/l	7.8 g/l
S Alb .	4 g/l	4.5 g/l	3.8 g/l
Toxicology Screen for organophosphorus	negative	negative	negative
Autoimmune screen panel	negative	negative	negative
ECG	NAD	NAD	NAD
CXR	NAD	NAD	NAD
CT brain	NAD	NAD	NAD

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