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EFFECT AND MANAGEMENT OF ACUTE DICHLORVOS POISONING IN WISTAR RATS

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ABSTRACT
Dichlorvos; organophosphorus pesticide is among the most widely used pesticides for insect control. In Nigeria and most other developing countries it is used indiscriminately by people with little or no knowledge of its toxic effects as a household and agricultural insecticide. The acute effect and antidotal therapy of dichlorvos was studied in laboratory animals. The LD_{50} in rats was determined to be 28.28 mg/kg i.p, with acute poisoning symptoms of micturation, restlessness, pupil constriction, respiratory distress and convulsion. Atropine was found to be the most effective antidote as it significantly ($P < 0.05 – 0.001$) reduced all symptoms of poisoning and gave 100% survival rate. There was however no significant difference between the animals treated with atropine alone and those treated with combination of atropine and diazepam. The results also showed that diazepam significantly reduced symptoms like restlessness ($P < 0.05$), pupil constriction and convulsion ($P < 0.001$).

Key Words: Dichlorvos, Acute Poisoning, Antidotal Therapy, Atropine, Diazepam

INTRODUCTION

Dichlorvos (2,3-dichlorovinyl dimethyl phosphate) is one of the classes of insecticides referred to as organophosphates used to control households and stored products insects. It is effective against mushroom flies, aphids, spider mites, caterpillars, thrips, and white flies in greenhouse, outdoor fruits, and vegetable crops (Lotti, 2001). Therapeutically, dichlorvos is used as a fumigant or to treat a variety of parasitic worm infections in dogs, livestock and humans. It acts against insects as both a contact and a stomach poison (Lotti, 2001).

Dichlorvos pesticide self-poisoning is an important clinical problem in the developing world, and kills an estimated 200 000 people every year (Michael, *et al.,* 2008). Concentrates of dichlorvos is mildly irritating to skin and may cause localized sweating, involuntary muscle contractions and burning sensations or actual burns (Aaron, 2001). When inhaled, the first effects are usually respiratory and may include bloody or runny nose, coughing, chest discomfort, difficult or short breath, and wheezing due to constriction or excess fluid in the bronchial tubes. Eye contact will cause pain, bleeding, tears, pupil constriction, and blurred vision. Following exposure by any route, other systemic effects may begin within a few minutes or be delayed for up to 12 hours. These may include pallor, nausea, vomiting, diarrhea, abdominal cramps, headache, dizziness, eye pain, blurred vision, constriction or dilation of the eye pupils, tears, salivation, sweating, and confusion. Severe poisoning will affect the central nervous system, producing incoordination, slurred speech, loss of reflexes, weakness, fatigue, involuntary muscle contractions, twitching, tremors of the tongue or eyelids, and eventually paralysis of the body extremities and the respiratory muscles. In severe cases there may also be involuntary defecation or urination, psychosis, irregular heart beats, unconsciousness, convulsions and coma. Death may be caused by respiratory failure or cardiac arrest (Michael, *et. al,* 2008).

Repeated or prolonged exposure to dichlorvos may result in the same effects as acute exposure including the delayed symptoms. Other effects may include impaired memory and concentration, disorientation, severe depressions, irritability, confusion, headache, speech difficulties, delayed reaction times, nightmares, sleepwalking and drowsiness or insomnia. An influenza-like condition with headache, nausea, weakness, loss of appetite, and malaise has also been reported (Clark, 2002 and Michael, *et. al,* 2008).

In Nigeria, especially the northern part, dichlorvors is traded under different names such as Nuvan, Sniper, Pia-pia (Hausa) and is handled and used as a household insecticide indiscriminately. The objective of this study is to determine the effective antidotal therapy of acute dichlorvos poisoning.

MATERIALS AND METHODS

Animals: Thirty three adult Wistar rats (150-200 g) of both sexes, maintained at the animal house, Pharmacology Department, Bayero University, Kano were used for the experiments. The animals were fed with standard feed (Vital feeds) and water *ad libitum*.

Chemicals: Sniper® (active ingredient: 2,3-dichlorovinyl dimethyl phosphate, 1000g/L. manufactured by Hubei Sanonda Co. Ltd, China), Atropine sulphate, Diazepam (Valium(R)) were used. All solutions were prepared fresh to desired concentrations with distilled water just before use.

Acute toxicity test
Acute toxicity (LD_{50}) values were estimated using Lorke's method (1983). In phase one, three groups of three rats each, were treated with 1, 10, and 100 mg/kg dichlorvos intraperitoneally (*i.p)* respectively. The animals were observed for clinical signs of toxicity and death for 24 hr. In the second phase, four (4) fresh animals were each treated with 20, 40, 60, and 80 mg/kg dichlorvos (*i.p)* respectively. The animals were observed for clinical signs of toxicity and death for 24 hr. The LD_{50} was then calculated as the geometric mean of the highest non-lethal and lowest lethal dose.

Antidotal therapy
Four groups of five rats were weighed and placed in four different cages. The first group which served as control was given 30 mg/kg dichlorvos. The second group received 30 mg/kg dichlorvos followed immediately with Atropine sulphate (5 mg/kg). The third and fourth groups were poisoned with same dose of dichlorvos followed immediately by diazepam (1 mg/kg) and combination of atropine (5 mg/kg) + diazepam (1 mg/kg) respectively. The rats were observed for effectiveness of the therapies based on the symptoms and number of survivals for 3 hours. The symptoms were scored according to severity as mild (1), moderate (2) or severe (3) on 3-point scale.

Statistical analysis: Results were expressed as mean **+** SEM. The significance of difference between means was determined by the Student's t-test and results were regarded as significant when $P < 0.05$.

RESULTS

Acute toxicity studies
Acute toxicity test using Lorke's method indicated LD_{50} value of dichlorvos to be 28.28mg/kg *i.p* in rats. Symptoms of acute toxicity observed were micturition, restlessness, pupil constriction, respiratory distress and convulsion (Table 1).

Antidotal therapy
The symptoms of the acute poisoning i.e. pupil constriction, restlessness, respiratory distress and convulsion were severe in the control group and least in atropine treated groups (Table 1). The percentage survival was 0% in the control group while the treated groups recorded 100% survival rate (Table 2).

Table 1: Symptoms of Acute Dichlorvos Poisoning (mean ± SEM)

Group	Micturition	Restlessness	Respiratory Distress	Pupil Constriction	Convulsion
Control	2.20 ± 0.20	3.00 ± 0.00	2.80 ± 0.20	3.00 ± 0.00	2.40 ± 0.25
Atropine	0.60 ± 0.25[a]	1.00 ± 0.32[b]	0.80 ± 0.45[a]	0.40 ± 0.23[c]	0.00 ± 0.00[c]
Diazepam	1.20 ± 0.38[ns]	1.40 ± 0. 25[a]	1.60 ± 0.40[ns]	0.80 ± 0.02[c]	0.00 ± 0.00[c]
Atropine + Diazepam	0.40 ± 0.25[a]	0.80 ± 0. 20[c]	1.30 ± 0.23[a]	0.50 ± 0.42[b]	0.00 ± 0.00[c]

n = 5 a - $P < 0.05$, b - $P < 0.005$, c - $P < 0.001$, ns – not significant

Table 2: Percentage Survival of Acute Dichlorvos Poisoning

Group	Number of Death	Percentage Survival
Control	5	0
Atropine	0	100
Diazepam	0	100
Atropine + Diazepam	0	100

n = 5

DISCUSSION

Dichlorvos is an organophosphate pesticide that acts by inhibiting the cholinesterase enzyme in mammalian tissues (Iyaniwura, 1991). Compared to poisoning by other organophosphates, dichlorvos causes a more rapid onset of symptoms, which is often followed by a similarly rapid recovery (Erdman, 2004). This occurs because dichlorvos is rapidly metabolized and eliminated from the body. Persons with reduced pulmonary (lung) function, convulsive disorders, liver disorders, or recent exposure to cholinesterase inhibitors will be at increased risk from exposure to dichlorvos. Alcoholic beverages may enhance the toxic effects of dichlorvos. High environmental temperatures or exposure of dichlorvos to visible or UV light may enhance its toxicity (Clark, 2002). Dichlorvos is highly toxic by inhalation, dermal absorption and ingestion (Clark, 2002). Because dichlorvos is volatile, inhalation is the most common route of exposure. As with all organophosphates, dichlorvos is readily absorbed through the skin.

The LD_{50} of dichlorvo intraperitoneally was 28.28 mg/kg and symptoms observed after acute poisoning were micturition, restlessness, pupil constriction manifested by bulging of the eye ball, respiratory depression and convulsion (Table 1). These symptoms might be due to the inhibitory action of dichlorvo on both brain and plasma cholinesterase enzyme leading to accumulation of acetylcholine at the post junction nerve endings. In the animals that died, the death may be due to respiratory failure or cardiac arrest and this was produced within minutes after administration of the poison.

The effectiveness of the antidotal therapy was based on the mean number of symptoms alleviated and the percentage survival produced. The antidotes were administered immediately after poisoning because the effectiveness of any antidotal therapy in cases of poisoning depends on how soon the antidote is administered. Atropine was found to significantly ($P < 0.05 - 0.001$) reduce all symptoms of poisoning compared to diazepam. There was however no significant difference between the animals treated with atropine alone and those treated with combination of atropine and diazepam (Table 1). The results also showed that diazepam significantly reduced symptoms like restlessness ($P < 0.05$), pupil constriction and convulsion ($P < 0.001$).

All the three antidotal groups recorded 100% survival while the control group recorded 0%. Death in the control group might be due to excessive stimulation of muscarinic sites and as atropine has both peripheral and central antimuscarinic actions, it effectively antagonized the muscarinic actions of acetylcholine. Diazepam also alleviated the symptoms of restlessness and convulsion in the rats and was able to calm them. The effectiveness of diazepam in the antidotal therapy could be attributed to its sedative, central muscle relaxant and anticonvulsant effects. The anticonvulsant and other CNS effects of benzodiazepines have been suggested to be due to mimicking of the putative inhibitory neurotransmitter, γ-aminobutyric acid (GABA) pathway in the brain, and of glycine in the spinal cord synapses (Henrikson, 1998).

CONCLUSION

The LD_{50} value obtained showed dichlorvos to be highly toxic and atropine alone was the most effective antidote compared to diazepam and atropine-diazepam combination as it significantly alleviated all the symptoms of acute poisoning and produced 100% survival.

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