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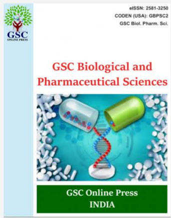


(RESEARCH ARTICLE)

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# Effect of chlorpheniramine on acute dichlorvos poisoning in wistar rats

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## Abstract

**Introduction**: Pesticide poisoning is a serious public health concern worldwide. According to WHO, about 3 million cases occur every year, resulting in more than 250,000 deaths. In response to the problems of unavailability of antidotes and cost in sub-Saharan Africa, this research set out to investigate chlorpheniramine, a cheap and readily available over the counter (OTC) antihistamine for possible antidotal effects on rats acutely poisoned with dichlorvos.

**Methodology**: The antidotal and protective effect of chlorpheniramine a $H_1$ antihistamine on acute toxicity by dichlorvos, an organophosphorus insecticide in wistar rats was investigated and compared with atropine, the standard antidote. Chlorpheniramine (2mg/kg, 4mg/kg, and 8mg/kg), atropine (0.4mg/kg, 0.8mg/kg, and 1.6mg/kg) and dichlorvos (4mg/kg) were all administered intraperitoneally. Dichlorvos at a dose of 4mg/kg induced acute toxicity in the rats observed as tremor, convulsion, defecation, straub tail, recumbence and gasping.

**Results**: Chlorpheniramine significantly ($p<0.05$) decreased the occurrence of acute signs of toxicity and also delayed the time of onset of signs of poisoning. Chlorpheniramine also prevented death of the animals with 100% survival rate after 2- 24hours of dichlorvos poisoning. Chlorpheniramine also reduced the toxicity score as compared to the control after acute toxicity testing for 14days.

**Conclusion**: The results suggests that chlorpheniramine possesses antidotal effects against dichlorvos induced toxicity in wistar rats comparable to atropine, the standard antidote and showed an additive positive antidotal effect when administered in combination with atropine.

**Keywords:** Dichlorvos; Chlorpheniramine; Antidote

## 1. Introduction

Agro-chemicals like pesticides, herbicides, fungicides etc. are popularly used by farmers to boost productivity and reduce pest infestation on their products. However, these chemicals may be toxic and affect human health negatively. They are also sometimes used in the household as pesticides. (Mahesh, Gowdar & Venkatesh, 2013)

Organophosphate poisoning is reported to be the most common cause of poisoning in the world, approximately 3 million poisonings per year leading to about two hundred and fifty deaths (Eddleston, 2019).

Dichlorvos is commonly used as a household insecticide for pest control and also in storing products from insects. Due to its toxicity, it has been banned in so many countries, such as in the EU since 1998, and most recently banned in Nigeria due to its widespread use for suicide. Sadly, this chemical is still widely used in sub-Saharan Africa. The commonest brand in Nigeria being Sniper®.

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Exposure to dichlorvos, which is an acetylcholinesterase inhibitor can lead to cholinergic crisis characterized by salivation, lacrimation, urination, defecation, gastric cramps, emesis (SLUDGE), however the manifestations of organophosphorus poisoning goes beyond the above mentioned. Neurological manifestations such as acute paralysis, ataxia, dystonia, lethargy, to mention but a few also occur (Bird & Grayzel, 2014).

Chlorpheniramine is one of the most commonly used antihistamines, it is a $H_1$ receptor antagonist (Sumit, Ajay, Preetha and Atul, 2012). $H_1$ receptor antagonists inhibit erythrocyte cholinesterase in vivo and plasma cholinesterase in vivo and in vitro in experimental animals such as horses and mice (Mohammad, Mousa and Hasan, 2012). Chlorpheniramine has antimuscarinic properties resembling that of atropine, which is the standard antidote for organophosphorus poisoning (Mousa, 2009).

The purpose of this study was to evaluate the antidotal effect of chlorpheniramine in rats acutely poisoned with dichlorvos.

## 2. Material and methods

### 2.1. Drugs

Atropine (IV) and chlorpheniramine (IV) were obtained from Alpha Pharmacy limited, G.R.A, Port Harcourt. Dichlorvos (Sniper ®) was purchased from I.T Johnson chemicals shop, hospital road Port Harcourt.

### 2.2. Experimental animals

Thirty wistar rats of both sexes, weighing 200-300g were purchased from the Department of Pharmacology Animal House, Faculty of Basic Clinical Sciences, University of Port Harcourt, Rivers state, Nigeria. They were allowed to acclimatize for two weeks and were housed in cages (5 animals per cage). The animals had free access to food and water. European Union Parliament and the Council on the handling of laboratory animals for scientific purposes (2010/63/EU) was used for this study.

## 3. Experimental design

### 3.1. A Pilot Study to determine dose of dichlorvos that would not cause death of animals.

The aim of this study was to observe the acute signs of toxicity of dichlorvos poisoning and not to use death as a measurement of toxicity. The intraperitoneal $LD_{50}$ of dichlorvos in rats (24mg/kg) as reported in previous studies was found to cause death of animals (Adeoti,*et al*,2017). The use of death as a measure of toxicity has been discouraged by the UNESCO bioethics committee. The parameter of toxicity used in this research work was observation of physical signs of toxicity such as defaecation, straub tail, tremor, convulsion, and recumbence. In addition, hepatic toxicity was also used to establish toxicity of dichlorvos:

This study was performed in groups of three animals each. The animals were weighed and dichlorvos administered intraperitoneally as follows:

- The first group received dichlorvos at a dose of 4mg/kg.
- Group two received dichlorvos at a dose of 8mg/kg.
- Group three received dichlorvos at a dose of 16mg/kg.
- Group 4, control received distilled water only

The animals were observed for clinical signs of toxicity for 24hours.

### 3.2. Antidotal Therapy

After establishing the safe dose of dichlorvos to be used for this study as 4mg/kg, this dose was used for the antidotal studies, the selection of doses of the antidotes, atropine and chlorpheniramine were based on preliminary experiments and on the literature (Mohammad *et al* 2002, Mousa *et al*, 2009)

5 groups of five rats each were weighed and placed in five different cages;

- Group A received dichlorvos only at a dose of 4mg/kg

- Group B received 3 doses of chlorpheniramine (2mg/kg, 4mg/kg and 8mg/kg respectively, 5 animals per dose) administered 5 minutes after dichlorvos administration (Liu *et al*,2008)
- (3) Group C received 3 doses of chlorpheniramine (2mg/kg, 4mg/kg and 8mg/kg, 5 animals per dose) in combination with atropine (1.6mg/kg), 5 minutes after dichlorvos administration.
- Group D received atropine alone, at 3 doses of 0.4mg/kg, 0.8mg/kg and 1.6mg/kg (5 animals per dose), given exactly 5minutes after dichlorvos administration
- Group E was given chlorpheniramine alone at doses of 2m/kg, 4mg/kg and 8mg/kg respectively, 5 animals per dose and this was given five minutes before dichlorvos administration.

The animals were observed for acute signs of toxicity for a 24hour period. The signs of toxicity observed were; tremor, convulsion, defaecation, gasping, recumbence and straub tail (Mousa, 2009)

Toxicity scores were calculated by adding the percentage of occurrence of acute signs of toxicity by the method of Al-Baggou and Mohammad, 1999. (1. 1-25%: 2. 26-50%: 3. 51-75%: 4. 76-100%).

### 3.3. Statistical analysis

Statistical analysis was done using IBM SPSS version 21. ANOVA was employed for comparing the mean intervals for different groups. Groups means together with standard errors of mean (SEM) were calculated and test groups result weighed against control. The p-values less than 0.05 ($p<0.05$) were deemed significant.

### 3.4. Ethical consideration

Ethical clearance was obtained from the University of Port Harcourt research ethics committee.

## 4. Results

**Table 1** Pilot studies showing onset of toxic symptoms, time and percentage of death following dichlorvos administration

| Group | Treatment | Time of onset of toxic symptoms(seconds) | Time of death(seconds) | %Death |
|---|---|---|---|---|
| 1 | Dichlorvos 4mg/kg | 57.00±3.72 | .00 | .00 |
| 2 | Dichlorvos 8mg/kg | 35.00±1.79 | 61.00±3.3 | 66.67 |
| 3 | Dichlorvos 16mg/kg | 10.00±8.1 | 10.00±8.1 | 100.00 |
| 4 | Distilled water | .000 | .000 | .000 |
| | | | | |

**Table 2** Effect of Low Dose Chlorpheniramine (2mg/kg) on Time of Onset of toxicity Symptoms in Dichlorvos Treated Rats

| Groups | Time of Onset(s) |
|---|---|
| D | 57.00±3.79 |
| DC | 528.3333±14.24* |
| DA | 561.6667±7.26* |
| DAC | 560.0000±5.77* |

*=The mean difference is significant at $p < 0.05$, n=5

Where, D = Dichlorvos alone, DC = Dichlorvos + Chlorpheniramine, DA = Dichlorvos + Atropine, DAC = Dichlorvos + Atropine + Chlorpheniramine

**Table 3** Effect of Medium Dose Chlorpheniramine (4mg/kg) on Time of Onset of Signs of toxicity in Dichlorvos Treated Rats

| Groups | Time of Onset(s) |
|---|---|
| D | 82.0000±7.00 |
| DC | 870.3333±32.99* |
| DA | 1239.3333±44.74* |
| DAC | 1289.3333±39.18* |

*=The mean difference is significant at $p < 0.05$, n=5
Where, D = Dichlorvos alone, DC = Dichlorvos + Chlorpheniramine, DA = Dichlorvos + Atropine, DAC = Dichlorvos + Atropine + Chlorpheniramine

**Table 4** Effect of High Dose Chlorpheniramine (8mg/kg) on Time of Onset of Signs of Acute Toxicity in Dichlorvos Treated Rats

| Groups | Time of Onset(s) |
|---|---|
| D | 25.0000±3.21 |
| DC | 731.0000±17.04* |
| DA | 2091.0000±49.69* |
| DAC | 2160.0000±34.03* |

*=The mean difference is significant at $p < 0.05$, n=5
Where, D = Dichlorvos alone, DC = Dichlorvos + Chlorpheniramine, DA = Dichlorvos + Atropine, DAC = Dichlorvos + Atropine + Chlorpheniramine

**Table 5** Summary of Results of Time of onset of toxic symptoms

| Group | | 2mg/kg(seconds) | 4mg/kg(seconds) | 8mg/kg(seconds) |
|---|---|---|---|---|
| 1 | DC | 528.33±14.24* | 870.33±32.99* | 731.0±17.04* |
| 2 | DA | 561.66±7.26* | 1239.33±44.74* | 2091±49.69* |
| 3 | DAC | 560.0±5.77* | 1289.33±39.18* | 2160±34.03* |
| 4 | D | 57.00±3.79 | 82.00±7.00 | 25.00±3.21 |

*=The mean difference is significant at $p < 0.05$, n=5
Where, D = Dichlorvos alone, DC = Dichlorvos + Chlorpheniramine, DA = Dichlorvos + Atropine, DAC = Dichlorvos + Atropine + Chlorpheniramine

**Table 6** Effect of Chlorpheniramine (2mg/kg, 4mg/kg, 8mg/kg) on time of Onset of Signs of Toxicity in Dichlorvos Treated Rats (Pre-treatment)

| Groups | Time of Onset(s) |
|---|---|
| D | 57.0000±3.79 |
| 2mg/kg | 219.3333±6.94* |
| 4mg/kg | 314.0000±8.71* |
| 8mg/kg | 382.6667±11.05* |

*=The mean difference is significant at $p < 0.05$, Where D = Dichlorvos

**Table 7** Percentage Occurrence of acute signs of toxicity (Low Dose, 2mg/kg)(%)

| S/N | Group | Tremor | Convulsion | Recumbence | Gasping | Defecation | Straub Tail | Toxicity Score |
|---|---|---|---|---|---|---|---|---|
| 1 | Control | 100 | 100 | 100 | 100 | 80 | 80 | 24 |
| 2 | Dich+Chlor | 60 | 80 | 60 | 60 | 40 | 60 | 18 |
| 3 | Dich+Atrop+Chlor | 40 | 40 | 20 | 20 | 40 | 40 | 10 |
| 4 | Dich+Atrop | 60 | 60 | 60 | 20 | 80 | 40 | 16 |

**Table 8** Percentage Occurrence of acute signs of toxicity (Medium Dose, 4mg/kg)(%)

| S/N | Group | Tremor | Convulsion | Recumbence | Gasping | Defecation | Straub Tail | Toxicity Score |
|---|---|---|---|---|---|---|---|---|
| 1 | Control | 100 | 100 | 100 | 100 | 80 | 80 | 24 |
| 2 | Dich+Chlor | 40 | 60 | 60 | 40 | 20 | 40 | 13 |
| 3 | Dich+Atrop+Chlor | 20 | 20 | 20 | 0 | 0 | 20 | 6 |
| 4 | Dich+Atrop | 40 | 40 | 20 | 20 | 0 | 20 | 8 |

**Table 9** Percentage Occurrence of acute signs of toxicity (High Dose, 8mg/kg)(%)

| S/N | Group | Tremor | Convulsion | Recumbence | Gasping | Defecation | Straub Tail | Toxicity Score |
|---|---|---|---|---|---|---|---|---|
| 1 | Control | 100 | 100 | 80 | 100 | 80 | 80 | 24 |
| 2 | Dich+Chlor | 40 | 40 | 60 | 40 | 20 | 40 | 12 |
| 3 | Dich+Atrop+Chlor | 20 | 20 | 20 | 0 | 0 | 20 | 6 |
| 4 | Dich+Atrop | 40 | 40 | 20 | 20 | 0 | 20 | 8 |

## 5. Discussion

The signs of acute toxicity exhibited by the rats acutely poisoned with dichlorvos include; convulsion, gasping, defaecation, straub tail and tremor. This toxicity was observed due to the action of dichlorvos on the enzyme acetylcholinesterase. Dichlorvos renders acetylcholinesterase inactive leading to accumulation of acetylcholine in the neuronal synapses and neuromuscular junction (Singh & Khurana*,* 2009). When this occurs there is muscarinic and nicotinic overstimulation , leading to manifestations mentioned above as well as others such as vomiting, hypotension , sweating, tachycardia, coma, muscle weakness and paralysis to mention but a few ( Bird *et al,* 2014).

Chlorpheniramine (2mg/kg,4mg/kg,8mg/kg), a $H_1$ antihistamine was observed to reduce significantly the exhibition of acute signs of toxicity, and this is comparable to atropine, the standard antidote, it was observed that a combination of chlorpheniramine and atropine produced a more significant reduction of the acute signs of toxicity than when either agent was used alone. While both atropine and chlorpheniramine reduced the acute signs of toxicity by 40%, the combination of both reduced the signs of toxicity by 60%.

The major factor in organophosphate poisoning is the inhibition of acetylcholinesterase, however, there are many other non-cholinergic factors that contribute to the mortality and morbidity in organophosphate poisoning. This includes allergic reactions stimulated by antibodies and mast cell degranulation, leading to the release of inflammatory mediators such as histamine. The anti-inflammatory properties of antihistamines such as chlorpheniramine can play a beneficial role in cases of organophosphate poisoning (Banks and Lein, 2012). They also reported that some organophosphates may lead to anaphylaxis by stimulating mast cells and basophils to release autacoids e.g. Soman (Banks & Lein, 2012).

Chlorpheniramine (2mg/kg, 4mg/kg, 8mg/kg) significantly ($p<0.05$) reduced the severity of dichlorvos toxicity in a manner that is quite comparable to atropine, the standard antidote. This result is in line with the report of Mousa 2009, who reported that chlorpheniramine has a protective effect and may be of value in cases of dichlorvos poisoning in chicks resembling that of atropine (Mousa, 2009).

From the results, chlorpheniramine decreased the onset of action of acute signs of toxicity following administration of dichlorvos.

In this study, the antidotal effect of chlorpheniramine was compared with atropine by using the same route of administration and time of administration. It was also observed that the combination of atropine and chlorpheniramine delayed the onset of action of acute signs of toxicity far better than either agent alone and also reduced significantly the percentages of occurrence of the acute signs of toxicity.

## 6. Conclusion

This study concludes that chlorpheniramine possesses antidotal effect against dichlorvos induced toxicity in a manner comparable to atropine, the standard antidote.However, the combination of both atropine and chlorpheniramine may give optimum effect in dichorvos poisoning.

## Compliance with ethical standards

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### *Disclosure of conflict of interest*

The authors declare no conflict of interest.

### *Statement of ethical approval*

Ethical clearance was obtained from the University of Port Harcourt research ethics committee.

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