



(RESEARCH ARTICLE)



Acute toxicity profile of chlorpheniramine: Potential use as antidote to dichlorvos poisoning

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Abstract

Introduction: Pesticide poisoning is a serious public health concern all over the world. Alternative therapies for organophosphorus poisoning are being explored, and this could be very useful especially in emergency situations of antidote shortages. This study therefore set out to determine the effects of chlorpheniramine on the kidney and liver function in dichlorvos poisoning.

Methodology: 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. Administration was done for 14 days, after which the animals were sacrificed under chloroform anaesthesia and blood samples collected for liver and kidney function tests.

Results: Chlorpheniramine and atropine offer some protective effects as they both reduced the raised values of the renal enzymes towards that of the control following dichlorvos poisoning. Chlorpheniramine and atropine counteracted the effect of dichlorvos on Na^+ , K^+ , Cl^- and HCO_3^- , by reducing the values closer to the normal range. However, the combination group significantly ($p < 0.05$) reduced the values and gave normal values of 147mmol/L (Na^+), 4.3mmol/L (K^+), 127mmol/L (Cl^-) and 18.3mmol/L (HCO_3^- respectively) when compared with the control. Chlorpheniramine raised the value closer to the normal range and gave a value of 4.82g/dl, though this increase was not statistically significant. Atropine gave a value of 5.0g/dl which is within the normal range. The combination group (Atropine + Chlorpheniramine) gave a value of 5.6g/dl which is within the normal range and the difference was statistically significant when compared to the negative control ($p < 0.05$). Chlorpheniramine reduced the elevation observed in the liver enzymes caused by dichlorvos poisoning (149.3U/L, 34.33U/L and 142.3U/L respectively).

Conclusion: This study concludes that chlorpheniramine has protective property on the liver and kidney against dichlorvos toxicity.

Keywords: Dichlorvos; Chlorpheniramine; Acute Toxicity

1. Introduction

The management of OP poisoning begins first with ABC (Airway, Breathing (ventilation), and circulation. Oxygen is given and intravenous fluids are also administered while monitoring for the risk of development of pulmonary oedema (Tibbut, 2011). The standard drugs for management of OP poisoning include: Atropine, which blocks the muscarinic effects of acetylcholine. In addition, Oximes such as pralidoxime chloride are beneficial when given shortly after exposure to organophosphorus compounds, they act by reactivating cholinesterase. However, recent reviews have shown that oximes may not be beneficial, though there is a possibility that certain groups of patients might benefit (Eddleston & Chowdhury, 2015).

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Histamine is a biogenic monoamine which is secreted from mast cells. It was first synthesized in 1907. When mast cells are activated, they undergo an anaphylactic or piecemeal degranulation dependent or independent mediator secretion, resulting in fast or slow release of soluble mediators e.g. histamine, chemokines, serine proteinases and growth factors. Histamine plays a very significant role in a number of physiological processes, including induction of inflammatory reactions, regulation of gastric acid production, vasodilation, smooth muscle contractions and neurotransmission. Antagonists of histamine receptors (H₁ & H₂) are the most widely prescribed drugs worldwide. A number of studies have shown its role in OP poisoning where inflammation is a major cause of death and disability. (Shreesh *et al*, 2014).

Chlorpheniramine is one of the most commonly used antihistamines, it is a H₁ receptor antagonist (Sumit, Ajay, Preetha and Atul, 2012).

2. Material and methods

2.1. Drugs

Atropine (IV) and chlorpheniramine (IV) were obtained from Alpha Pharmacy limited, Government Residential Area, 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. The directive (2010/63/EU) of the European Union Parliament and the Council on the handling of laboratory animals for scientific purposes was used for this study.

3. Experimental design

Determination of the Effect of Dichlorvos on Liver /Kidney Function (Acute Toxicity Test)

Animals were grouped into five, with five animals per group;

- Group A received dichlorvos (4mg/kg) alone
- Group B received dichlorvos (4mg/kg) and chlorpheniramine (4mg/kg)
- Group C received dichlorvos (4mg/kg) and atropine (1.6mg/kg)
- Group D received dichlorvos (4mg/kg), in combination with chlorpheniramine (4mg/kg) and atropine (1.6mg/kg)
- Group E, control, received distilled water only

Administration was done for 14days, after which the animals were sacrificed under chloroform anaesthesia and blood samples collected for liver and kidney function tests.

3.1. Sample collection

After treatment, the rats were sacrificed under chloroform anaesthesia. Blood samples were collected from the jugular vein and put into tubes (heparinised and non-heparinised) for liver and kidney function tests.

Data from kidney and liver function test were analysed with LSD multiple comparison (post-hoc test) to compare various treatment groups with the control group as well as standard drugs.

3.2. Ethical consideration

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

4. Results

Table 1 Effect of Dichlorvos, Chlorpheniramine and Atropine on Liver function in Rats Acutely Poisoned with Dichlorvos.

Groups	AST(U/L)	ALT(U/L)	ALP(U/L)
D	181.6667±15.90*	57.6667±1.45*	175.0000±20.21*
DC	149.3333±19.22	34.3333±3.48	142.3333±1.47
DA	127.3333±25.40	30.0000±6.35*	112.0000±22.34
DAC	100.6667±19.80	28.6667±6.49*	101.3333±19.32
Control	77.3333±9.94	24.6667±3.18	78.6667±8.76

*=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 2 Effect of Chlorpheniramine on Liver Markers in Rats Acutely Poisoned with Dichlorvos

Groups	TP(g/dL)	ALB(g/dL)	TB(mg/dL)	CB(mg/dL)
D	4.76667±0.26*	3.43333±0.39*	17667±0.009*	.07833±0.007*
DC	4.82000±0.06*	3.40000±0.06	.14333±0.01	.06533±0.008
DA	5.01000±0.01	3.70000±0.06	.11667±0.02	.06000±0.006
DAC	5.60000±0.20*	3.80000±0.12	.10000±0.03*	.05600±0.002
Control	5.66667±0.38	3.80000±0.17*	.10167±0.03*	.04567±0.01*

*=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 Chlorpheniramine on Renal Function in Rats Acutely Poisoned with Dichlorvos

Groups	Ur(mg/dL)	Cr(mg/dL)	Cl(mmol/L)
D	24.16667±2.94	62333±0.11	127.00000±0.58
DC	21.00000±0.58	.38333±0.042*	120.66667±1.76*
DA	19.53000±0.017	.30667±0.03*	117.00000±1.15*
DAC	17.70000±0.115*	.29000±0.04*	106.00000±0.58*
Control	16.96667±3.09	.32333±0.04	102.23333±0.96

*=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 Chlorpheniramine on Electrolytes in Rats Acutely Poisoned with Dichlorvos

Groups	Na(mmol/L)	K(mmol/L)	HCO ₃ (mmol/L)
D	160.00000±1.15*	6.13333±0.23*	12.66667±1.45*
DC	157.00000±0.5*	5.00000±0.29*	13.66667±1.20*
DA	150.00000±1.73*	4.70000±0.06*	15.33333±0*
DAC	147.00000±1.15*	4.30000±0.12*	18.33333±1.45*
Control	145.33333±2.90	4.00000±0.44	21.00000±1.53

*=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

5. Discussion

Aspartate transaminase (AST), alkaline phosphatase (ALP), Alanine transaminase (ALT) are very useful biomarkers of liver injury. (Adeoti *et al*, 2017). AST and ALT in serum are used to diagnose body tissues especially the heart and the liver if injury exists or not. When the tissues of the heart and liver are damaged, these enzymes are released into the blood and raise the serum enzyme level. ALP on the other hand detects blocked bile ducts, liver damage or bone disorders. Increased ALP is indicative of damaged liver cells.

Chlorpheniramine (2mg/kg,4mg/kg,8mg/kg) significantly 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 and also prevented the death of the animals, it also showed protective effects on hepatic and renal biomarkers, as well as on plasma electrolytes.

Other antihistamines such as diphenhydramine, and promethazine have been reported to reduce dichlorvos-induced toxicosis in chicks as well as in rats (Mohammad *et al*, 2002). Adetoye *et al*, (2018), reported that promethazine alone or in combination with atropine has potent antidotal effect in dichlorvos poisoning. Mohammad *et al*, 2012, also suggested that diphenhydramine may have protective and ameliorative effects similar to atropine against organophosphate poisoning in chicks (Mohammad *et al*, 2012).

After acute toxicity studies for 14days, chlorpheniramine showed protective effects on renal and hepatic biomarkers. Aspartate transaminase (AST), alkaline phosphatase (ALP), Alanine transaminase (ALT), bilirubin, and serum electrolytes were significantly elevated by dichlorvos. Chlorpheniramine alone and in combination with atropine showed protective effects by countering the effects of dichlorvos and bringing the values closer to the normal range.

6. Conclusion

In conclusion, this study suggests that chlorpheniramine, an antihistamine, has protective effects comparable to atropine, the standard antidote and could be used as a cheaper, readily available alternative to atropine in cases of dichlorvos 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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