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Research Article

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Toxicological effect of Promethazine on the Kidney, liver and heart of Wistar Rats

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Abstract This study evaluated the effect of Promethazine, Atropine and Promethazine + Atropine on kidney, liver and heart functions of wistar rats. A total of 25 adult rats were used. The animals were divided into 5 groups with 5 rats per group. Group V, the positive control group received normal feed and water. Group W received only dichlorvos 15mg/kg. Group X received dichlorvos 15mg/kg and Promethazine 1.5mg/kg. Group Y was given dichlorvos 15mg/kg and Atropine 1.6mg/kg and Group Z was given dichlorvos 15mg/kg, Promethazine 1.5mg/kg and Atropine 1.6mg/kg. On day 14, blood samples were collected for kidney and liver function tests and tissue samples obtained from the heart for histopathological analysis. Results revealed that Kidney and Liver function test showed significant changes in Urea, Creatinine, Aspartate transaminase (AST) and Alanine Transaminase (ALT) when compared with the animals that received feed and water only and the animals treated with only dichlorvos. Photomicrographs of the heart of rats that received promethazine alone showed normal histology. This study therefore concludes that Promethazine alone or in combination with Atropine has potent antidotal effect on dichlorvos poisoning. At the doses studied, this drug was not found to be hepatotoxic or nephrotoxic.

Keywords liver cirrhosis, portal hypertension syndrome, varicose veins of the esophagus, prevention, endoscopic ligation

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 [1]. It acts by inhibiting synaptic acetylcholinesterase which is also its mechanism of toxicity. Dichlorvos pesticide self-poisoning is an important clinical problem in the developing world, and kills an estimated 200,000 people every year [2]. Organophosphate poisoning therefore is an existing serious concern in Nigeria as poisoning by this compound is on the increase. This is as a result of its frequent use by farmers for pest control as well as household pest control. Dichlorvos has also been recorded to be hepatotoxic and nephrotoxic.

Promethazine is a neuroleptic medication and first-generation antihistamine of the phenothiazine family used to treat allergy symptoms, nausea and vomiting after surgery and to prevent motion sickness. This research study therefore on drug repurposing set out to assess the effect of promethazine, atropine and promethazine + atropine on kidney, liver and heart function to find out if either after treatment would be hepatotoxic or nephrotoxic and hence to determine how safe it is after treatment course.

Methodology

25 rats weighing between 220g- 300g obtained from the department of Pharmacology animal house were used for this study. The rats were bred and maintained under suitable conditions, allowed an acclimatization period of two (2) weeks, housed in hygienic cages in groups of five and allowed free access to feed obtained from vital feeds UAC PLC and water *ad libitum*. The beddings were changed and cages cleaned out on alternate days. Animals were handled according to Helsinki declaration on animal care. The animals were divided into 5 groups, each consisting of 5 rats each. The groups included those for treatment and the control groups. Drugs were administered intraperitoneally via a 1ml syringe.

Determination of the Effects of Promethazine, Atropine and Promethazine + Atropine on the Kidney, Liver and Heart Function of Wistar Rats

This study spanned 3 weeks and was domiciled in the Department of Pharmacology, University of Port Harcourt, Animal house and Laboratory. A dose dependent toxicological evaluation of the effects of these individual drugs and their combinations on the liver function of rats was evaluated. This test was carried out on twenty-five (25) adult wistar rats. The animals were grouped into five (5) with five (5) rats per group. Drug administration was done intraperitoneally as follows

- Group V, the positive control, was given feed and water only
- Group W received only dichlorvos 15mg/kg
- Group X received dichlorvos 15mg/kg and was treated with Promethazine 1.5mg/kg
- Group Y received dichlorvos 15mg/kg and was treated with Atropine 1.6mg/kg
- Group Z received dichlorvos 15mg/kg and was treated with both Promethazine 1.5mg/kg and Atropine 1.6mg/kg

Sample Collection

After treatment with promethazine, atropine and promethazine + atropine, all the rats were sacrificed under chloroform anesthesia. The animals were put in a dessicator with cotton wool soaked in chloroform for about 2-3 minutes. Blood was obtained by cardiac puncture using sterile syringe and needle. The blood was divided into two portions. One portion was collected into heparinised sample bottle in order to obtain whole blood for renal function test. The other portion was placed into a non-heparinized tube, allowed to stand for one hour to clot at room temperature, and further spun at 2000 rpm for 30 minutes and serum removed with syringe and needle. The serum was then used for liver function test

Results

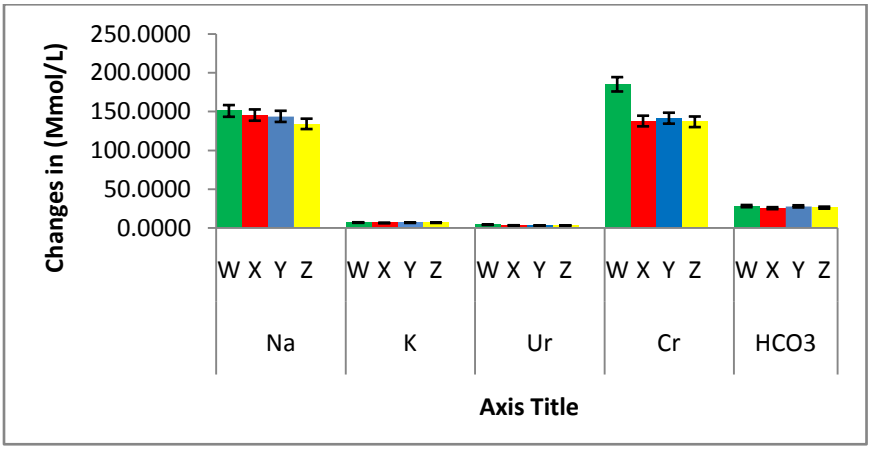

Figure 1: Comparative changes in electrolytes (Na = Sodium, K = Potassium, Ur = Urea, Cr = Creatinine, HCO_3 = Bicarbonate)

Key:
Animal that received feed and water only
W = Exposure to only dichlorvos
X = Exposure to dichlorvos and treatment with only promethazine
Y = Exposure to dichlorvous and treatment with only atropine
Z = Exposure to dichlorvous and treatment with Promethazine and Atropine
Results are expressed as mean±SEM, the superscript (*) means significant difference with respect to Group V (normal feed and water) and Group W (dichlorvos only) at P<0.05.

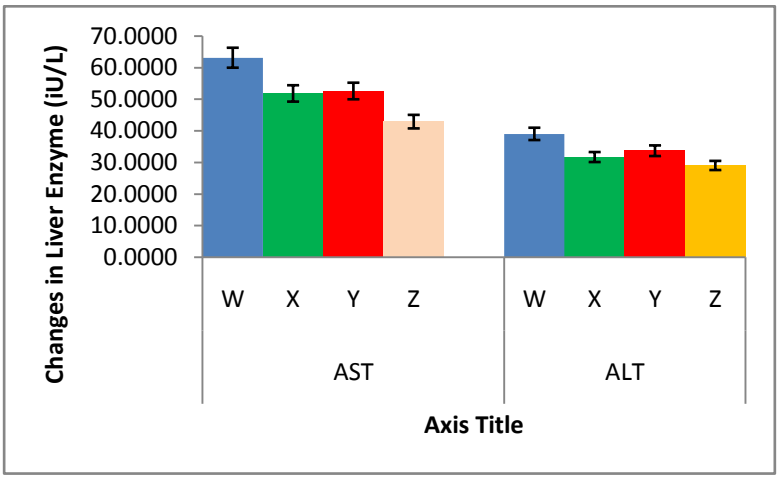

Figure 2: Comparative changes in liver enzymes (AST= Aspartate Transaminase, ALT = Alanine Transaminase

Key:
Animal that received feed and water only
W = Exposure to only dichlorvos
X = Exposure to dichlorvos and treatment with only promethazine
Y = Exposure to dichlorvous and treatment with only atropine
Z = Exposure to dichlorvous and treatment with Promethazine and Atropine
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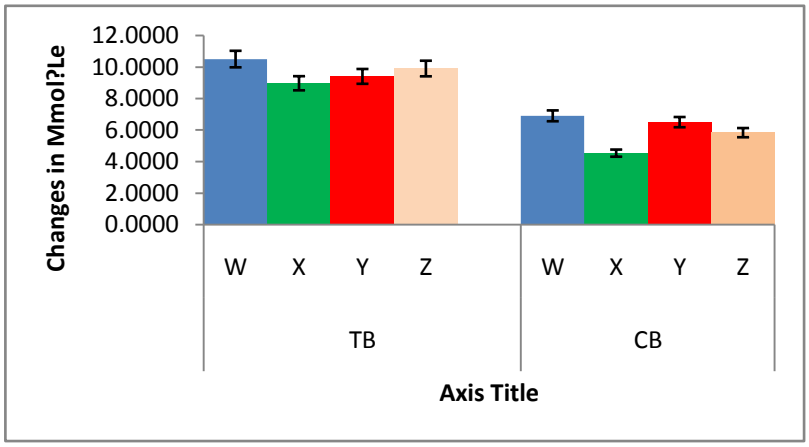


Figure 3: Comparative changes in Total Biluribin (TB) / Conjugated Biluribin (CB)

Key:
Animal that received feed and water only
W = Exposure to only dichlorvos
X = Exposure to dichlorvos and treatment with only promethazine

Y = Exposure to dichlorvous and treatment with only atropine
Z = Exposure to dichlorvous and treatment with Promethazine and Atropine
Results are expressed as mean±SEM, the superscript (*) means significant difference with respect to Group V (normal feed and water) and Group W (dichlorvos only) at P<0.05.

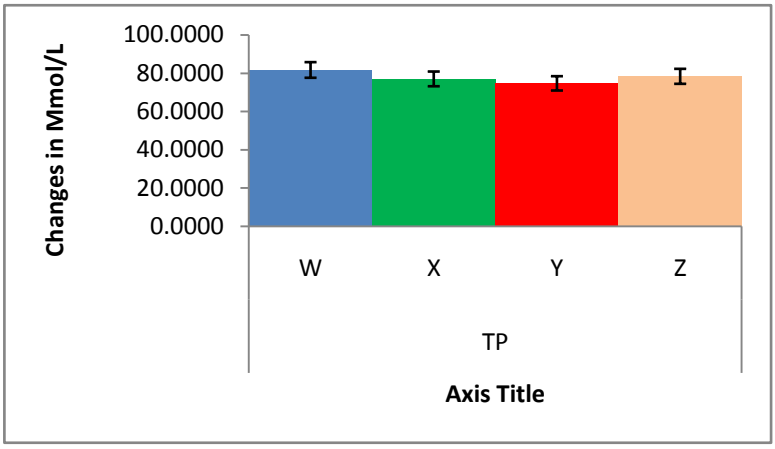
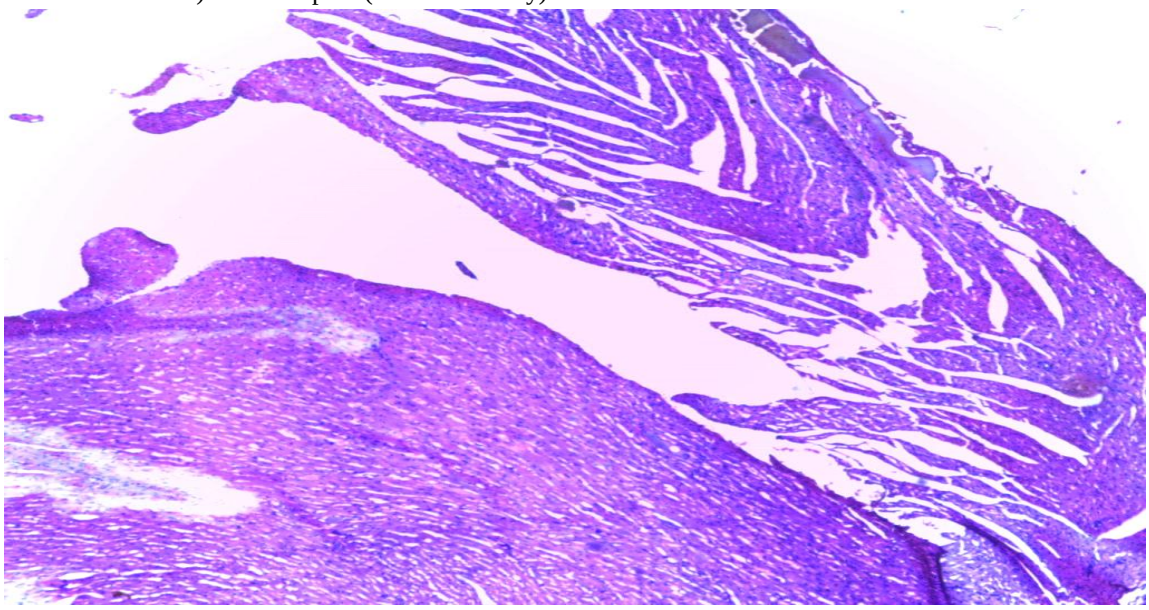


Figure 4: Comparative changes in Total Protein (TP)

Key:
Animal that received feed and water only
W = Exposure to only dichlorvos
X = Exposure to dichlorvos and treatment with only promethazine
Y = Exposure to dichlorvous and treatment with only atropine
Z = Exposure to dichlorvous and treatment with Promethazine and Atropine
Results are expressed as mean±SEM, the superscript (*) means significant difference with respect to Group V (normal feed and water) and Group W (dichlorvos only) at P<0.05.



Cardiac myocytes blood vessels

Figure 5: Photomicrograph of a normal heart showing cardiac myocytes and blood vessels. (H&E X200)

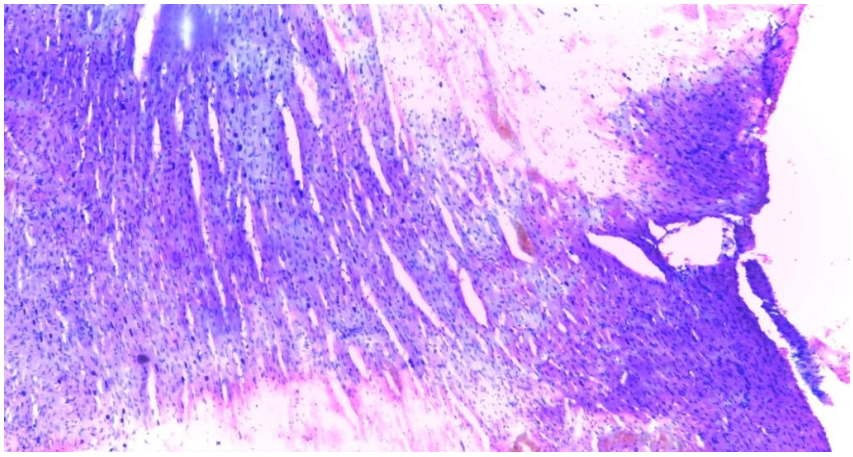


Figure 6: Photomicrograph of heart of test rats exposed to only dichlorvos showing congested vessels and areas of hemorrhage (H&E X200)

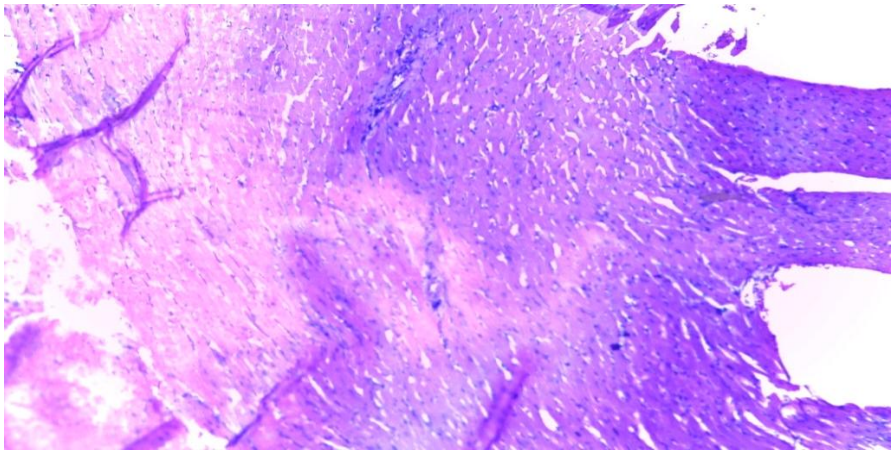


Figure 7: Photomicrograph of the Heart of test rats treated with Promethazine showing no obvious abnormality (H&E X200)

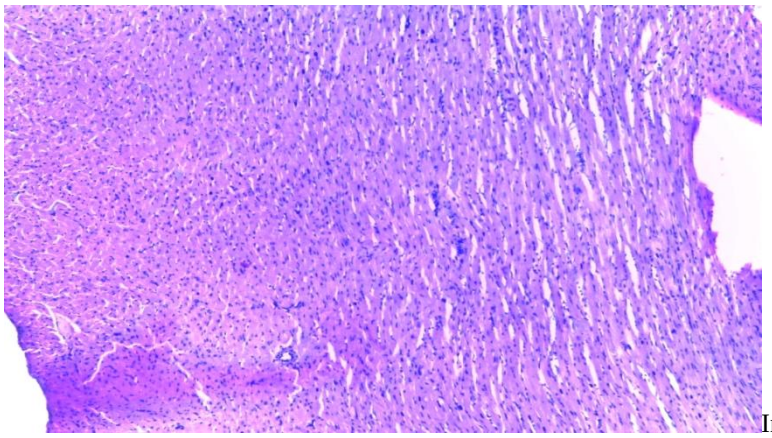
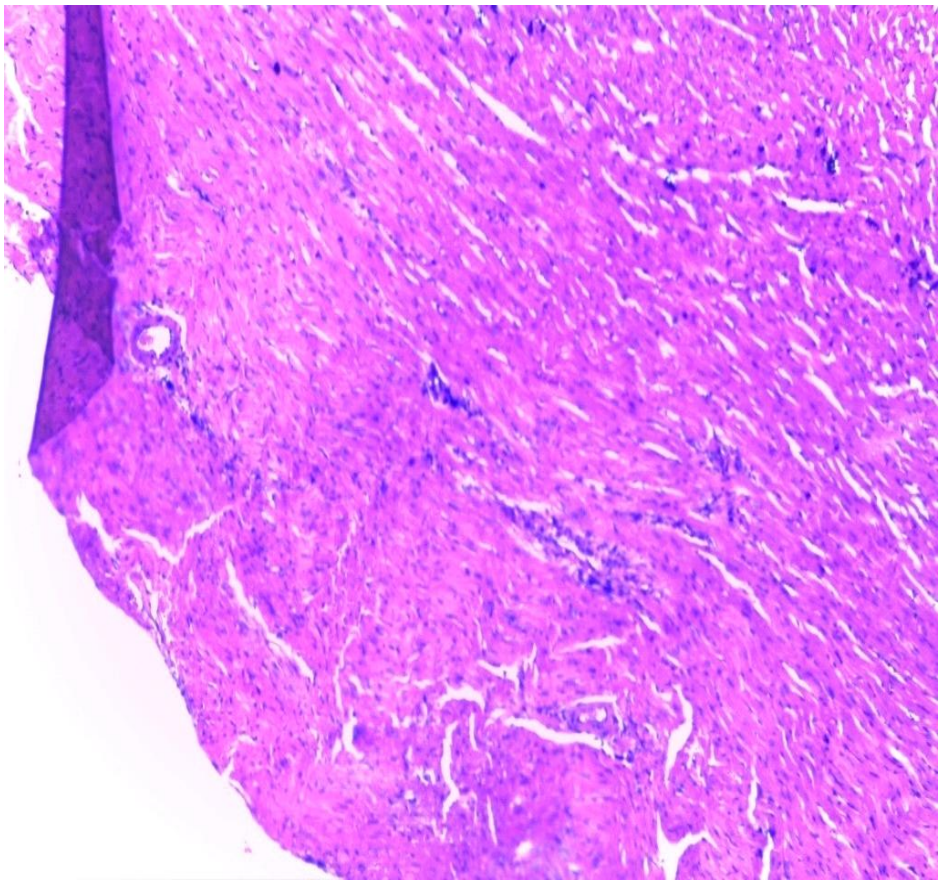

Inflammatory cells

Figure 8: Photomicrograph of heart of test rat treated with Atropine which shows mild inflammation of the myocytes. (H&E X200)



Inflammatory cells in myocytes

Figure 9: Photomicrograph of heart of test rat treated with Promethazine and Atropine which shows inflammation of myocytes. (H&E X200)

Discussion

The liver is the organ for metabolism of endogenous and foreign compounds. Blood is conveyed to the liver through the portal vein which carries blood containing digested nutrients from the GIT and the hepatic artery which carries oxygenated blood from the lungs. Liver enzymes AST and ALT are often used as biomarkers of liver injury since they are produced by hepatocytes into the extracellular space. The statistically significant elevations in plasma AST and ALT recorded in the present research showed organophosphate as a hepatotoxic substance. This agrees with earlier observations on dichlorvos by Eisenkraft *et al* [3]. Serum creatinine and blood urea have typically been employed for diagnosis of acute kidney injury. The significant elevations in plasma urea and creatinine levels observed implied possible organophosphate nephrotoxicity. A former investigation by Erdman *et al.,* [4] reported also increases in serum creatinine and urea levels. It was demonstrated that elevations in serum kidney parameters (creatinine, electrolytes and urea) are the biomarkers for acute nephritic damage [5]. Moreso increases in plasma hepatic enzymes (alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and bilirubin (TB and CB)) are indicators for acute hepatocellular impaired functions [6]. This research recorded statistically significant elevations in plasma AST, ALT, Creatinine and urea after the animals were treated with dichlorvos. The effect of promethazine treatment, atropine treatment and promethazine + atropine treatment following a two week treatment course on renal and hepatic parameters were investigated in adult Wistar rats. The results revealed statistically significant ($p<0.05$) difference in Urea, Creatine, Aspartate transaminase (AST), Alanine transaminase (ALT) and Conjugated Bilirubin (CB) in the animals treated with promethazine only. The test also recorded non-significant changes in plasma Na, HCO_3, Total bilirubin and Total Protein levels compared to the

control. The results also revealed statistically significant ($p<0.05$) difference in Na, Urea, Creatinine, Aspartate transaminase (AST) and Alanine transaminase (ALT) in the animals treated with promethazine + atropine and non-significant changes in K, HCO_3, Total bilirubin, Conjugated bilirubin and Total protein in the same group of animals treated with promethazine + atropine.

Conclusion

This study therefore concludes that Promethazine alone might be cardioprotective also at the doses studied this drug was not found to be hepatotoxic or nephrotoxic.

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