

Research Article

Acute Exposure to Dichlorvos and Cypermethrin on Fasting Blood Glucose, Insulin and Liver Enzymes in Male Wistar Rats

Isehunwa Grace Olufunmilayo^{*} , Oyelade Ruth Oluwakemi, Shittu Sheu-Tijani ,
Alada Akinola AbdulRasak 

Department of Physiology, College of Medicine, University of Ibadan, Ibadan, Nigeria

Abstract

Dichlorvos (DDVP) and Cypermethrin (CP) are major pesticides used in agriculture to control agricultural pests and household insects and pests. Exposure to DDVP and CP is associated with the risk of developing diabetes. However, there are few studies that have reported the dose effects of DDVP and CP exposure on blood glucose levels and liver enzymes. This study investigated the effects of acute exposure to low and high doses of DDVP and CP on fasting blood glucose, insulin and liver enzymes in male Wistar rats. Thirty-five (35) male Wistar rats weighing between 170 g-200 g were used in the study. They were randomly divided into seven groups of 5 animals per group (N=5). Groups 1, 2 and 3 animals received distilled water, 4 mg/kg and 8 mg/kg DDVP orally and respectively for 7 days. Animals in groups 4, 5, 6 and 7 received CP 12 mg/kg, CP 24 mg/kg, combined DDVP (4 mg/kg) and CP (12 mg/kg), combined DDVP (8 mg/kg) and CP (24 mg/kg) orally and respectively for 7 days. After 7-day treatment and overnight fasting, body weights, fasting blood glucose, insulin level and levels of liver enzymes of the rats were measured. Homeostasis model assessment of insulin resistance (HOMA-IR) was determined. Blood glucose was measured using modified glucose oxidase method. Serum levels of insulin and liver enzymes Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Alkaline Phosphatase, (ALP) were determined using ELISA. The results of the study showed that acute exposure to low and high doses of Dichlorvos, Cypermethrin, combined DDVP and CP caused significant increase in fasting blood glucose, and insulin levels compared with the control in the rats. However, dichlorvos at low and high doses produced more significant increases in blood glucose and insulin levels compared with low and high doses of CP, and combined DDVP and CP. Also, acute exposure to Dichlorvos and Cypermethrin caused significant decrease in body weights of the animals and increased concentration of liver enzymes. In conclusion, the study showed that acute exposure to low and high doses of DDVP and CP caused insulin resistance and fasting hyperglycemia. Acute exposure to low and high low doses of DDVP and CP also caused liver damage, increase in concentrations of liver enzymes and reduction in body weight of rats.

Keywords

Dichlorvos, Cypermethrin, Insulin, Fasting Blood Glucose, Liver Enzymes, Body Weight

^{*}Corresponding author: gisehunwa@gmail.com (Isehunwa Grace Olufunmilayo)

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1. Introduction

One of the global problems occurring in developing countries especially in Nigeria is indiscriminate use of insecticides [14]. DDVP and CP are pesticides used in agriculture to eliminate crop diseases and insect infestations. Studies have shown that more than 3 million people suffer from pesticide poisoning every year [35]. It has been reported that over 5.6 billion pounds of pesticides are used annually to improve agricultural output [9]. Pesticide pollution is a form of environmental contamination that has posed risk to both human and animal health. Acute pesticide poisoning has been reported to cause harm within a short time that can be life threatening [35]. Studies in animals have shown that organophosphate insecticides can alter glucose homeostasis and in humans cause poisoning and hyperglycemia [21]. Exposure to pesticides has been reported to cause metabolic diseases associated with insulin resistance, diabetes, obesity and metabolic syndrome [7]. However, the study of Seesen et al [29], showed no significant association between organophosphate pesticide exposure and insulin resistance in pesticide sprayers and general population but observed correlation between the use of personal protective equipment and work practices and the level of organophosphate exposure in pesticides sprayers. Pesticides such as Dichlorvos (DDVP) and Cypermethrin (CP) are important insecticides, commonly used by farmers in Nigeria, and over the world. Due to its indiscriminate agrarian use, humans are exposed to these pesticides in dairy and meat products, beverages, cereals and water [20]. Also, unregulated domestic use, especially for fumigation, is another source of exposure to humans of different ages. In 2021, it was reported that cereals from Nigeria were banned from exportation to Europe, due to high concentration of Cypermethrin in the farm produce, which may be harmful to human health [25]. Animal studies have shown that Cypermethrin and Dichlorvos have adverse effects on glucose metabolism. Organophosphates have been reported to cause neurotoxicity, endocrine toxicity, immunotoxicity, reproductive toxicity, genotoxicity and cellular oxidative imbalance and impaired glucose homeostasis. Early studies have shown that ALT activities are upregulated in gluconeogenic conditions and may be implicated in the development of diabetes [27]. In-

creased serum enzyme concentrations are markers of liver damage [22]. Exposure to DDVP has been linked to liver injury in humans [35]. The rise in the burden of diabetes mellitus characterized by imbalance in glucose homeostasis calls for concern. Earlier studies have reported the association between pesticides (DDVP and CP) and glucose homeostasis. However, there is limited information on the exact mechanisms by which DDVP and CP affect glucose metabolism. Since most people use these pesticides to control pests in homes and preserve food, this study was designed to investigate acute exposure to low and high low doses of DDVP and CP on fasting blood glucose, insulin levels and liver enzymes in male Wistar rats.

2. Materials and Methods

Thirty-five male Wistar rats weighing between (170-200 g) obtained from animal house, Department of Physiology, University of Ibadan, Ibadan were used in the study. They were acclimatized for two weeks and had free access to standard rodent chow and clean water. The animals were randomly divided into 7 groups (N=5/group). Groups 1 (control), 11 and 111 received distilled water, DDVP (4 mg/kg), and DDVP (8 mg/kg) orally and respectively for 7 days. Animals in groups 1V, V, V1, and V11 received CP (12 mg/kg), CP (24 mg/kg), combined DDVP 4 mg/kg + CP (12 mg/kg) and combined DDVP 8 mg/kg + CP 24 mg/kg respectively and orally for 7 days. After 7-day treatment and overnight fasting, blood was collected from the tail of each animal for glucose determination using modified glucose oxidase method. Blood was collected through retro orbital sinus into plain bottles for determination of insulin and liver enzymes. Serum levels of insulin and liver enzymes ALT, AST, and ALP were determined using ELISA. The rat's body weight was measured with a digital weighing scale.

Homeostasis assessment of insulin resistance (HOMA-IR)

The HOMA-IR was calculated using the formular:

Homeostatic model assessment for insulin resistance (HOMA-IR) was calculated using the formular: [34]

$$\text{HOMA} - \text{IR} = \frac{\text{Fasting insulin level } (\mu\text{U/mL}) \times \text{Fasting glucose level (mg/ dL)}}{405}$$

Statistical analysis

All values given are mean $\pm$ S.E.M. of the variables measured. Values between two groups were assessed using students' t-test while One-way analysis of variance (ANOVA) was used to compare mean values in multiple groups. Differences were considered statistically significant at $p < 0.05$.

3. Results

Body weight

Acute exposure to low and high doses of dichlorvos and cypermethrin caused significant reduction ($p < 0.05$) in body weight of rats compared to control group (Figure 1).

Fasting blood glucose level

There was a significant increase ($p < 0.05$) in blood glucose levels of rats exposed to low and high doses of DDVP and CP compared to control rats (Figure 2). However, the low and high doses of dichlorvos produced a more significant increase in blood glucose level compared with low and high doses of cypermethrin (Figure 2).

Insulin levels

Serum insulin levels of rats exposed to low and high doses of DDVP and CP significantly increased ($p < 0.05$) compared with the control rats (Figure 3). Low and high doses of DDVP produced a more significant increase in serum insulin than the low and high doses of CP (Figure 3).

Liver enzymes

Acute exposure to low and high doses of DDVP and CP caused significant increase ($p < 0.05$) in the concentrations of liver enzymes AST, ALT, and ALP compared with control group (Table 1).

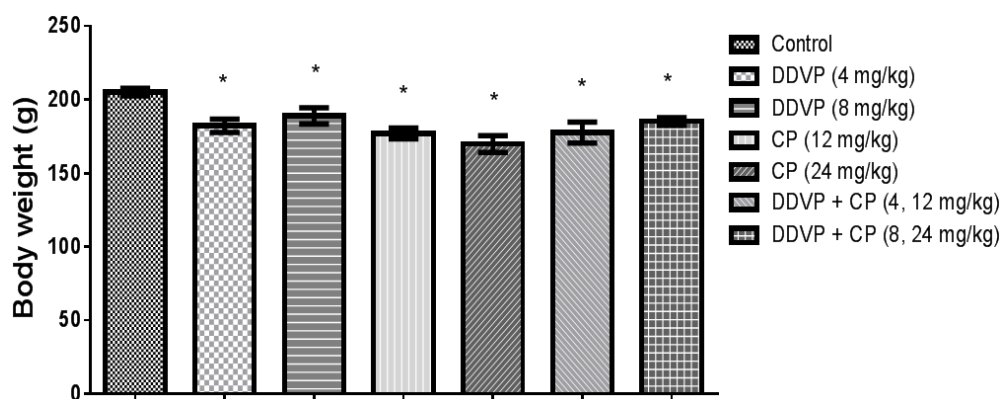


Figure 1. Effects of low and high doses of Dichlorvos and Cypermethrin on body weight in male Wistar rats. Values were expressed as mean $\pm$ S.E. ($n = 5$). *Significantly different from control (Control) at $P < 0.05$.

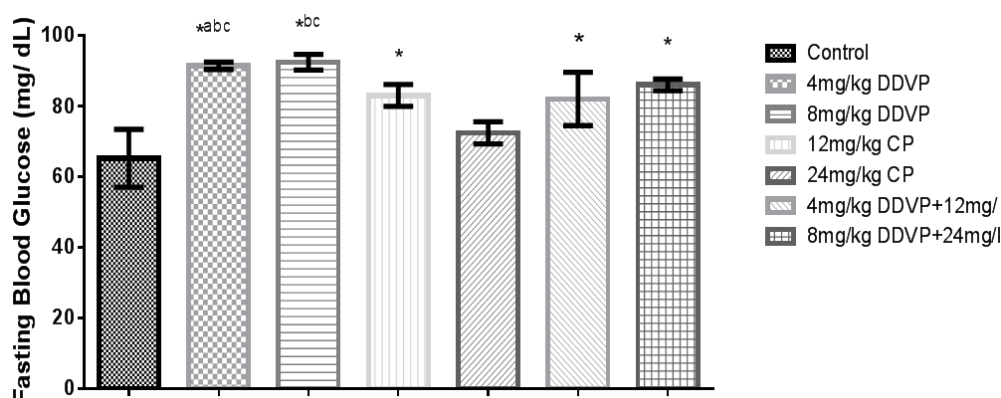


Figure 2. Effects of low and high doses of Dichlorvos and Cypermethrin on fasting blood glucose in male Wistar rats. Values were expressed as mean $\pm$ S.E. ($n = 5$). * $p < 0.05$ compared with Control, ^a $p < 0.05$ compared with 12 mg/kg CP, ^b $p < 0.05$ compared with 24 mg/kg CP, ^c $p < 0.05$, compared with combined 8 mg/kg DDVP + 24 mg/kg CP.

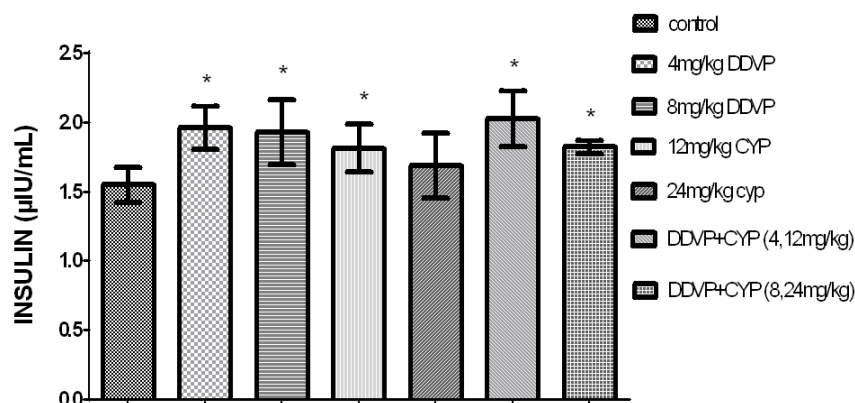


Figure 3. Effects of low and high doses of Dichlorvos and Cypermethrin on serum insulin level in male Wistar rats. Values were expressed as mean $\pm$ S.E. ($n = 5$). *Significantly different compared with control at $P < 0.05$.

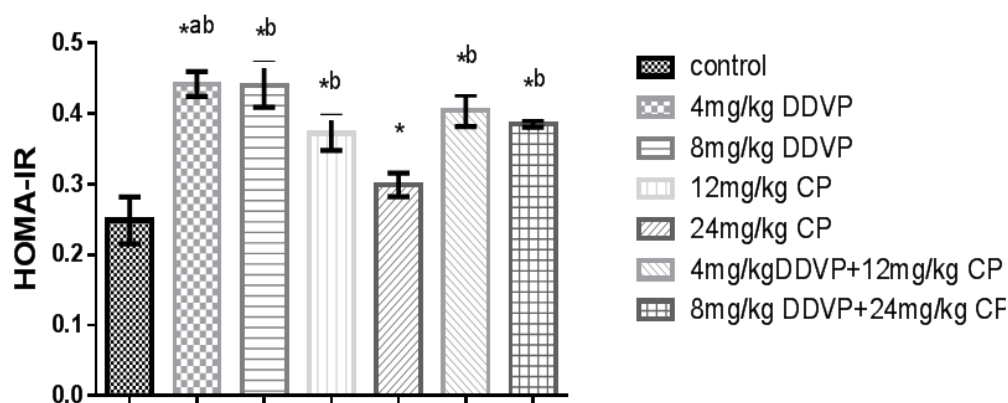


Figure 4. Effects of low and high doses of Dichlorvos and Cypermethrin on Homeostatic Model Assessment for insulin Resistance in male Wistar rats. Values were expressed as mean $\pm$ S.E. ($n = 5$). * $p < 0.05$ compared with Control, ^a $p < 0.05$ compared with 12 mg/kg, CP, ^b $p < 0.05$ compared with 24 mg/kg CP.

Table 1. Effects of low and high doses of Dichlorvos and Cypermethrin on liver enzymes.

(Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Alkaline Phosphatase, (ALP) in male Wistar rats.

Groups	Control	4 mg/kg DDVP	8 mg/kg DDVP	12 mg/kg CP	24 mg/kg CP	4 mg/kg DDVP + 12 mg/kg CP	8 mg/kg DDVP + 24 mg/kg CP
ALT (U/L)	59.39 $\pm$ 1.207	62.64 $\pm$ 1.307*	74.43 $\pm$ 1.712*	62.64 $\pm$ 1.307*	74.43 $\pm$ 1.712*	66.61 $\pm$ 2.036*	60.55 $\pm$ 1.033*
AST (U/L)	78.82 $\pm$ 1.278	82.64 $\pm$ 1.180*	80.43 $\pm$ 1.262*	82.64 $\pm$ 1.180*	80.43 $\pm$ 1.262*	84.10 $\pm$ 0.4610*	82.70 $\pm$ 1.946*
ALP (U/L)	51.72 $\pm$ 0.3975	52.93 $\pm$ 0.1978*	52.95 $\pm$ 0.3324*	54.58 $\pm$ 1.913*	53.73 $\pm$ 1.386*	52.67 $\pm$ 0.4113	52.16 $\pm$ 0.1596

Low and high doses of DDV, CP and combined DDVP and CP caused significant increase in the concentration of liver enzymes (ALT, AST and ALP).

Values were expressed as mean $\pm$ S.E. ($n = 5$). *Significantly different from control (Control) at $P < 0.05$

4. Discussion

The findings of the present study in which DDVP and CP caused fasting hyperglycemia in rats are consistent with previous studies [1, 5, 12, 13, 16]. The increase in glucose levels may be due to reduced glucose utilization and impaired tissue function [13]. The observed increase in fasting blood glucose might also be due to activation of adenylyl cyclase [32] and decreased activity of hepatic glucokinase [5, 28]. In rats, studies have shown that exposure to organophosphate compounds stimulated hepatic gluconeogenesis and glycogenolysis to meet increased energy requirements for detoxification and other involuntary muscular activities [30]. Exposure to organophosphates also stimulated liver and muscle glycolysis resulting in production of ATP for body energy [2, 12]. Organophosphates have been reported to cause endocrine toxicity and impair glucose homeostasis. Association between organophosphate poisoning and severe hyperglycemia has

been reported [30]. Studies in rats showed that exposure to organophosphate compounds such as malathion caused hyperglycemia through hepatic gluconeogenesis and glycogenolysis to meet increased energy demands [17]. Exposure to DDVP has been reported to inhibit gene expression associated with glucose metabolism and disrupt liver energy metabolism in Zebrafish [10]. The study of Zhang et al [36] reported high blood glucose levels and homeostasis model assessment of insulin resistance index in rats treated with alpha cypermethrin. The observed fasting hyperglycemia in the present study may be due to reduced glucose utilization because of impaired tissue function caused by exposure to dichlorvos and cypermethrin. The present study also showed that low and high doses of DDVP produced more significant increase in fasting blood glucose and insulin levels than CP.

In the present study, the body weight of the animals exposed to DDVP and CP decreased. Acute exposure to low and high doses of DDVP and CP resulted in weight loss. The weight loss may be due to the inability to use glucose for

energy production caused by decreased insulin action thus leading to higher consumption of fat and protein. Increased protein catabolism has been reported to generate amino acids for gluconeogenesis which can lead to muscle waste and weight loss [31]. In the present study, there was a reduction in body weight of animals exposed to DDVP and CP. The observed decrease in body weight of rats exposed to DDVP and CP might also be due to reduction in dietary intake and reduced energy intake. This is consistent with studies in mice [11] and rats [13] in which administration of deltamethrin and alpha-cypermethrin respectively caused reduction in body weight of animals. The reduced body weight of animals exposed to DDVP and CP might also be a consequence of the toxic effects of DDVP and CP on the central nervous system which controls feeding and water intake and regulates endocrine function [11]. There was also report of weight loss in rats treated with alpha cypermethrin [36].

The observed increase in insulin levels in the present study suggests that DDVP and CP altered glucose homeostasis and caused hyperglycemia through impaired insulin sensitivity. This was supported by higher index observed Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) and consistent with study in mice exposed to chlorpyrifos [19]. The pancreatic beta cells are stimulated to produce insulin in response to glucose rise and are the master regulator of blood glucose homeostasis [23]. In the present study, the observed increase in fasting blood glucose and insulin levels suggest that DDVP and CP did not affect the secretory function of pancreatic islet beta cells [33]. The significant increase in HOMA-IR in the present study suggests that exposure to DDVP and CP affected and decreased glucose uptake in insulin-sensitive tissues in the rats. It has been reported that CP treatment in high caloric diet-fed mice induced insulin resistance and decreased hepatic glucose uptake through impaired translocation of glucose transporter GLUT2 leading to reduced glycogenesis and increased gluconeogenesis [33]. This agrees with previous studies in rats exposed to organophosphate such as malathion [26]. The reduced insulin sensitivity may account for higher blood glucose and insulin levels observed in the present study. The observed hyperglycemia may be through insulin resistance caused by detrimental effects of DDVP and CP on insulin sensitivity. Insulin resistance leads to decrease in glucose utilization by insulin target tissues leading to diabetes [18]. In contrast, Seesen et al [29] did not observe any significant association between organophosphate exposure and insulin resistance in pesticide sprayers and non-farm workers.

Serum enzyme levels are used to measure the overall health status of an individual particularly in liver injury and stress. Small amounts of intracellular enzymes are found in the blood due to normal cell turnover [15]. The increased blood concentrations of AST, ALT, and ALP observed in the present study after 1 week exposure to DDVP and CP suggests that both low and high doses of DDVP and CP are harmful and toxic to the liver. Liver enzymes concentrations increase after

they are released in response to hepatocyte injury [24]. Similar observations have been reported in previous studies [6, 8, 24]. Elevation of liver enzymes in rats exposed to DDVP, CP, Chlorpyrifos and Deltamethrin has been reported [4]. There have been also reports of an increase in the levels of AST and ALT in rats exposed to DDVP [3] and rats exposed to alpha-cypermethrin [16]. Higher ALT activity is associated with insulin resistance, obesity, diabetes and metabolic syndrome [27]. In the present study, the increased concentrations of liver enzymes AST, ALT and ALP observed may be due to damage of liver caused by toxic effects of DDVP and CP.

In conclusion, the study showed that acute exposure to low and high doses of CP and DDVP caused fasting hyperglycemia and insulin resistance, which may contribute to the development of diabetes. The present study also showed that low and high doses of dichlorvos produced a more significant increase in blood glucose and insulin levels than low and high doses of cypermethrin. Acute exposure to low and high doses of DDVP and CP also caused a reduction in the body weight of the animals and an increase in the concentration of liver enzymes. This study suggests that acute exposure to DDVP and CP at low and high doses predisposes to diabetes through insulin resistance and causes liver damage. Therefore, exposure to DDVP and CP should be minimized.

Abbreviations

DDVP	Dichlorvos
CP	Cypermethrin
AST	Aspartate Aminotransferase
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
HOMA-IR	Homeostasis Model Assessment of Insulin Resistance

Author Contributions

Grace Olufunmilayo Isehunwa: Data curation, Formal Analysis, Investigation, Software, Visualization

Ruth Oluwakemi Oyelade: Conceptualization, Project administration, Software, Supervision, Validation, Visualization, Writing – original draft X, Writing – review & editing

Shehu-Tijani Shittu: Conceptualization, Data curation, Funding acquisition, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing

Akinola Abdul Rasaqi Alada: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Resources, Software, Supervision, Visualization, Writing – original draft, Writing – review & editing

Conflicts of Interest

The authors declare no conflicts of interest.

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