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Toxicological Effects of Propoxur on Electrolyte Balance in Pigeon *(Columba livia domestica)*

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Abstract: Propoxur is a carbamate insecticide used for household control of flies, ants, aphids, mosquitoes, cockroaches and millipedes. Despite the increasing use of propoxur in Egypt, there is no complete information on the toxicity of this insecticide in birds. In this study we measured serum levels of sodium, potassium, calcium, phosphorus, bicarbonate, urea, creatinine, and uric acid as biomarkers to assess the toxic effects of propoxur on electrolyte balance and the quality of kidneys for maintaining this balance. The bird employed in the present study is the rock pigeon (*Columba livia domestica*), weighing between 320 – 380g. Birds were classified into four groups each consists of 5 animals as follow:1- Control group, this group, non-treated pigeons, were not subjected to oral administration of the insecticide. 2- Three doses group, pigeons in this group treated with a repeated oral dose (1/10 LD_{50}) of propoxur for three consecutive doses. 3- Six doses group, pigeons in this group treated with a repeated oral dose (1/10 LD_{50}) of propoxur for six consecutive doses. 4 – Nine doses group, Pigeons in this group treated with a repeated oral dose (1/10 LD_{50}) of propoxur for nine consecutive doses. (Two days interval between each two consecutive doses in treated groups) and birds were sacrificed after 24 hours after the last dose. Results of this study, showed significant increase in serum sodium, potassium, urea and uric acid, and significant decrease in venous blood bicarbonate, and non-significant changes in serum

levels of calcium, phosphorus and creatinine as a result of subchronic dosage with propoxur.

Keywords: Propoxur, Carbamate, Electrolyte, Kidney, Toxicity.

1. INTRODUCTION

Since the 20th century, thousands of organic pollutants have been produced and released into the environment [37]. Many of these chemicals that are released into the environment are extremely stable and persistent and pose a hazard to the wild living organisms that are exposed directly in their habitats. Persistent organic pollutants resists degradation, accumulate in aquatic and terrestrial ecosystems and also transported through air, water and migratory species and deposits in other places far from the place of their production [1].

Carbamates are a class of insecticides which have been used worldwide. Carbamates, e.g., propoxur, have similarity to organophosphates in inhibiting acetylcholinesterase, but there is a difference between carbamates and organophosphates, the carbamates are transient cholinesterase inhibitors and are hydrolyzed from the cholinesterase enzymatic site within 48 hours [2]. Thus, carbamate toxicity is shorter in duration compared to the organophosphates, although the mortality rates associated with exposure to these chemical classes are still similar [3]. Carbamates has lower toxicity and shorter half-life, thus it have been used widely in place of organophosphates, particularly for home uses. Cholinergic effects of propoxure were discussed by Moser et al [4]. In the study of Yadav et al [5], Oral administration of propoxur (10 mg/kg b.wt.) resulted in a significant reduction of brain and blood AChE activity.

Carbamates oxidative stress caused by generation of free radicals and changes in antioxidant enzymes as SOD and catalase and production of lipid peroxidation which is showed as increase in MDA [6]. The study of Waly et al. [7] concluded that exposure of animals to diazinon or propoxur are capable of including marked hazardous alterations. The influence of propoxur might also extend to general physiological and pathological condition, nutritional status, functions of hormones and metabolic process in liver, and also, the immune system [8].

Acute and chronic exposure to propoxur leads to adverse effects on memory and antioxidant status which expressed in the study of Mehata et al [9] as increase in MDA and reduction in GSH levels. Results of the study of Ruiz et al [10] suggest that intoxication with carbamates leads to reduction of GSH level and oxidative stress. However, the induction of the antioxidant enzyme GST produced by aldicarb sulfone and propoxur in CHO-K1 cells, suggests that the enzyme provides adequate protection to mammals cells through the detoxification of these carbamates. Studies on rats shown that sub-chronic intoxication with propoxur leads to suppression in immune system and oxidative stress. The study of Zafiropoulos et al [11], concluded that, organophosphate and carbamate poisonings leads to lethal cardiac complications leading to death and various arrhythmias which may be due to oxidative stress and oxidative modifications in the genomic DNA content of the cardiac tissues.

Biomarkers can be defined as measurable changes of cellular or biochemical compounds, structures or functions caused by xenobiotics, namely after exposure to environmental contaminants. Biological response can occur on molecular, cellular, tissue or organ level and can be measurable in biological systems such as tissues, cells and biological fluids [12]. These changes are related to the exposure or to the effects of

toxicants and have been successfully applied to monitor the presence and the effects of contaminants in various toxicological and ecotoxicological studies [13-15]. Monitoring the parameters of an initial change caused by the interaction of organism and xenobiotic compound can characterize the level of exposure or toxic effect [16]. Biomarkers can measure the health quality of organisms, and used as monitoring signals for particular or general stress [32]. In this study we measured serum levels of sodium, potassium, calcium, phosphorus, bicarbonate, urea, creatinine, and uric acid as biomarkers to assess the toxic effects of propoxur on electrolyte balance and the quality of kidneys for maintaining this balance.

2. MATERIALS AND METHODS

2.1. Experimental Animal: The bird employed in the present study is the rock pigeon (*Columba livia domestica*) which belongs to order columbiformes, weighing between 320 – 380g. Experimental birds purchased from local market of Benha city, Egypt. They were apparently healthy, active and free from any abnormalities. Birds were kept for one week under normal conditions of feeding with free access to water before experiments in order to assure their acclimatization.

2.2. Insecticide: The carbamate insecticide used in the present work was propoxur. The chemical names are: 2- isopropoxyphenyl–N–methyl-carbamate and 2-(1-methylethoxy) phenylmethyl carbamate). The common names are propoxur and PHC. Propoxur has also been called IMPC and IPMC. Ttrade names have included Baygon, Balttanex, Invisi-Gard, Propogon, Sendra, Sendran, Suncide, Tendex, Tugon, Fliegenkugel, Unden and Undene [17].

2.3. Dosage of propoxure: The required dose of propoxur was mixed with 1gm of wheat dough, formed as pellets, dried, and was given to pigeons by obligatory oral feeding.

2.4.-Methods

(A).Determination of LD_{50} of propoxur for pigeon (*Columba livia domestica*): Five groups of pigeons (7 birds each) were treated with a single oral doses of propoxur 30, 36, 42, 48, and 52 mg / kg body weight, respectively . The pigeons died were watched by the end of 24 hrs., and the mortality percentage was determined according to the method of Litchfield and Wilcoxon [18]. This experiment was repeated twice and the average of mortality was taken. The calculated median lethal concentration (LD_{50}) of propoxur for the rock pigeon, *Columba livia domestica* , at a period of 24 hrs. was 38.83 mg/kg body weight .

(a).Experimental Groups: Birds were classified into four groups each consists of 5 animals as follow:

(I). Control group: This group, non-treated pigeons, were not subjected to oral administration of the insecticide.

(II).Three doses group: Pigeons in this group treated with a repeated oral dose (1/10 LD_{50}) of propoxur for three consecutive doses. (two-day interval between each two consecutive doses) and birds were sacrificed after24 hours after the last dose.

(III).Six doses group: Pigeons in this group treated with a repeated oral dose (1/10 LD_{50}) of propoxur for six consecutive doses. (two-day interval between each two consecutive doses) and birds were sacrificed after24 hours after the last dose.

(IV).Nine doses group: Pigeons in this group treated with a repeated oral dose (1/10 LD_{50}) of propoxur for nine consecutive doses. (two-day interval between each two consecutive doses) and birds were sacrificed after24 hours after the last dose.

(B).Determination of Bicarbonate concentration

Blood sampling: For analysis of (HCO_3^-), birds were anaesthetized by ether inhalation. Venous blood samples were taken anaerobically from post caval veins by means of 1 ml tuberculin syringes with 18-22ψ gauge needles. Heparin was used as an anticoagulant (1000 USP units of heparin per 1 ml blood). The needle was held in a horizontal position with the blood vessels so that the blood flows into the syringe partially without coming into contact with the atmospheric air [19]. The syringe was sealed with a rubber cap and placed on ice water for a maximum period of ten minutes.

Analysis Bicarbonate concentration: For (HCO_3^-)**,** 238 M. Ciba Corning pH Blood Gas Analyzer was used to measure blood pH and carbon dioxide partial pressure (PCO_2) in mmHg, and calculate bicarbonate (HCO_3^-), the apparatus incorporates a calculator which accurately calculate values for anaerobic plasma, bicarbonate according to the Henderson-Hasselbaleh equation

$$\left(pH = pK + Log \frac{HCO_3^-}{\alpha\, PCO_2} \right)$$

Where pK is the negative logarithm of the H^+ concentration at which half of the carbonic acid molecules are associated and half dissociated and it equals 6.1, α is the solubility coefficient of CO_2 and it equals 0.03.

Blood sampling for other biochemical parameters: Blood samples were collected by making a puncture in the wing vein, large enough to ensure a free flow, making sure not to take the first drops which contain haemolysed blood, in non-heparinized tubes, and left overnight at 4°C to obtain a full separation of clott. Serum was obtained by centrifugation of the tubes at 5000 r.p.m. for 10 minutes then stored in deep freeze (at -20^0 C) for kidney function tests and electrolytes.

(C).Determination of Serum Sodium and Potassium Concentrations: Sodium and potassium ions were determined using Na^+ and K^+ filter of flame photometer (Jenway PFP7. ESSEX.UK.).

(D).Determination of Serum Calcium, Phosphorus, Urea, Creatinine, and Uric acid Concentrations:

Biochemical analysis for serum Calcium, Phosphorus, Urea, Creatinine, and Uric acid were performed using commercially available kits from Diamond Diagnostics Company (Egypt) and quantified according to the manufacturer's instructions.

2.5. Statistical Analysis: Data are expressed as mean ± SD. The level of statistical significance was taken at $P < 0.05$, using one way analysis of variance (ANOVA) test followed by Dunnett test to detect the significance of differences between each group and control. All analysis and graphics were performed by using graphPad Prism software version 5.

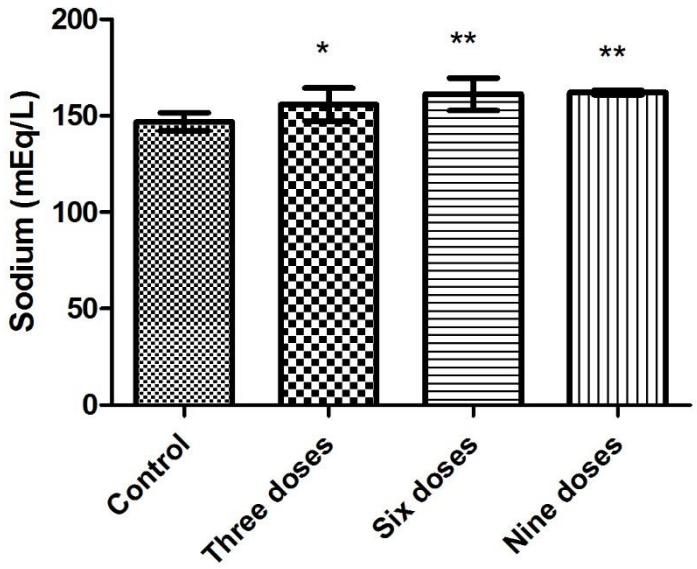
3. RESULTS

In this study, serum levels of sodium, potassium , calcium, phosphorus and venous blood bicarbonate were used to indicate effects of subchronic intoxication of propoxur (1/10 LD50) on electrolyte balance.

Measurements for serum urea, creatinine, and uric acid, were used as markers for kidney functions, as the kidneys are the main organs which maintain the electrolyte balance in the body. Sodium concentration in serum was affected by propoxur dosage for three doses and increased significantly ($P < 0.05$) by 6.1% compared to control and highly significant increase ($P < 0.01$) six and nine doses by 9.7% and 10.3% respectively as compared to control (F**igure 1**).

Serum potassium was affected by propoxur dosage with different degrees according to number of doses. It increased significantly in six doses group ($P < 0.05$) by 50.3% as compared to control, on the other hand, the effects are non-significant in three and nine doses groups (**Figure 2**). The changes of serum calcium and phosphorus did not show any significant changes as compared to control (F**igures 3, 4**). Venous blood bicarbonate were reduced in intoxicated groups after three, six and nine doses by -21.6%, -8.7%, and -12.3% respectively, as compared to control pigeons group (F**igure 5**).

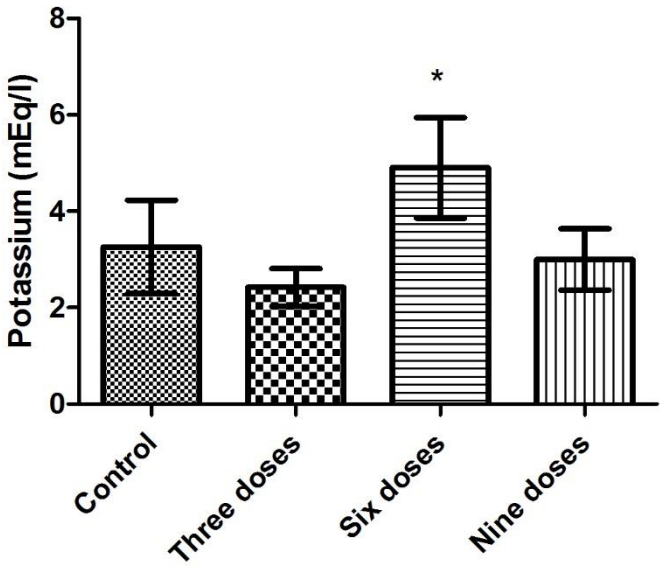
Figures (6, 7 and 8) illustrate the effects of repeated oral doses of proxour (1/10 LD_{50} each) on kidney function tests. Serum urea concentration was increased significantly in pigeons treated with a repeated dose (1/10 LD_{50}) of propoxur; after 3 doses, 6 doses 9 doses by percentages of increase 481%, 511% and 465% as compared to control pigeons group. Significant increase in serum uric acid concentration .in pigeons treated with repeated doses (1/10 LD_{50}) of propoxur; after 6 and 9 doses compared with control pigeons group by 32% and 20% respectively, as illustrated in F**igure (8)** as compared to control. There are no any significant changes were observed in serum creatinine concentration in all intoxicated groups (F**igure 7**).



(*) significant difference compared to control group ($P < 0.05$).

(**) highly significant difference compared to control group ($P < 0.01$).

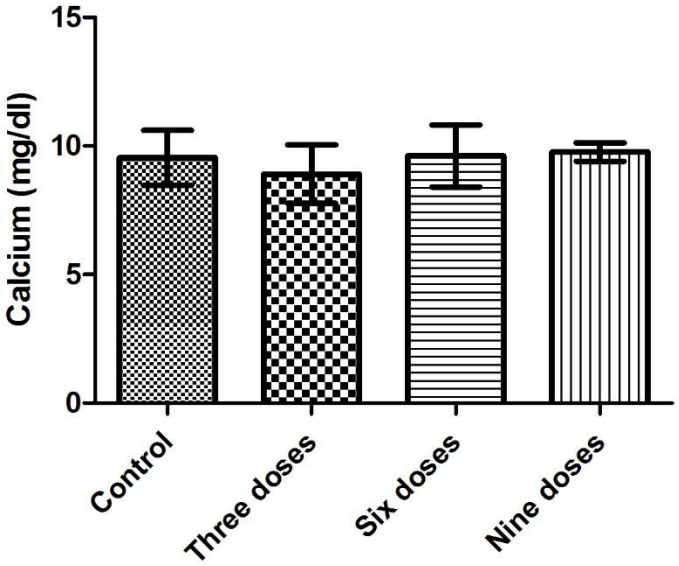
Figure 1: Serum sodium in pigeon as affected by subchronic oral dosage (1/10 LD50) of propoxur



(*) significant difference compared to control group (P < 0.05).

(**) highly significant difference compared to control group (P < 0.01).

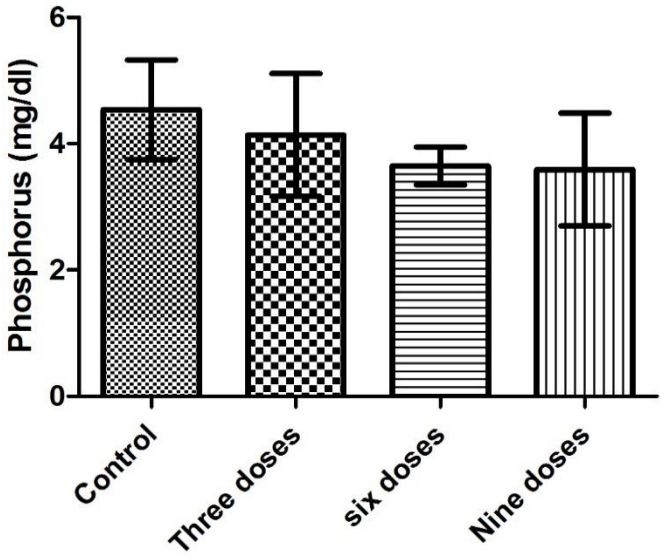
Figure 2: Serum potassium in pigeon as affected by subchronic oral dosage (1/10 LD50) of propoxur



(*) significant difference compared to control group (P < 0.05).

(**) highly significant difference compared to control group (P < 0.01).

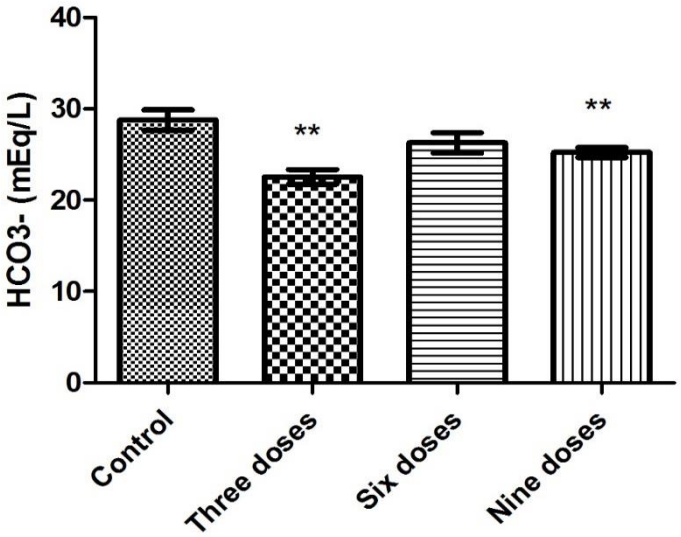
Figure 3: Serum Calcium in pigeon as affected by subchronic oral dosage (1/10 LD50) of propoxur



(*) significant difference compared to control group (P < 0.05).

(**) highly significant difference compared to control group (P < 0.01).

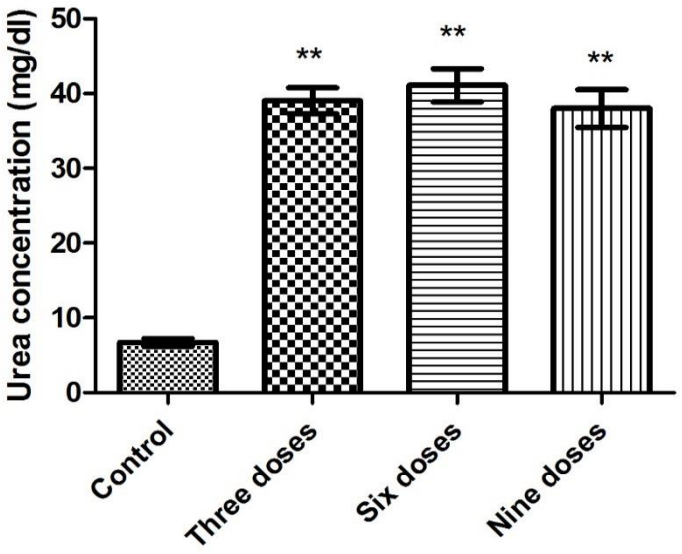
Figure 4: Serum Phosphorus in pigeon as affected by subchronic oral dosage (1/10 LD50) of propoxur



(*) significant difference compared to control group (P < 0.05).

(**) highly significant difference compared to control group (P < 0.01).

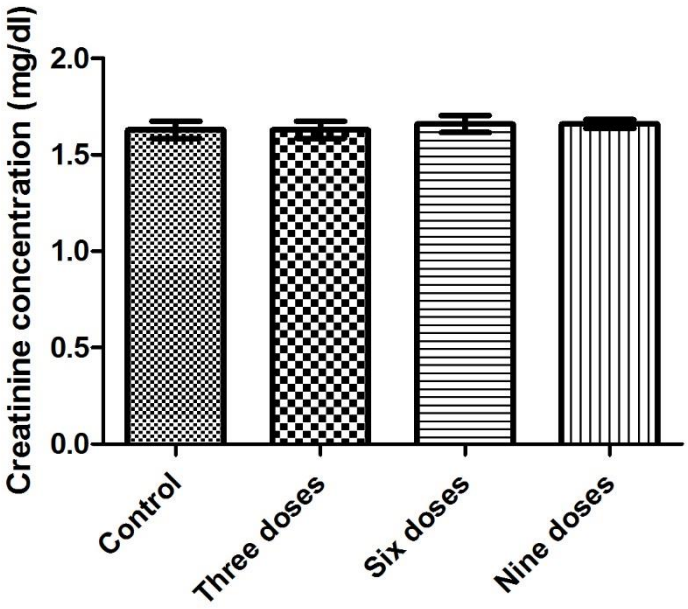
Figure 5: Venous blood Bicarbonate in pigeon as affected by subchronic oral dosage (1/10 LD50) of propoxur



(*) significant difference compared to control group (P < 0.05).

(**) highly significant difference compared to control group (P < 0.01).

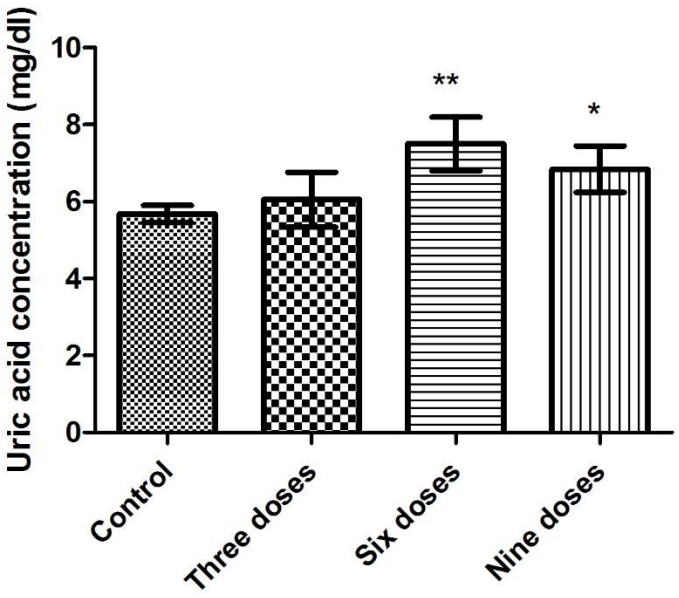
Figure 6: Serum Urea in pigeon as affected by subchronic oral dosage (1/10 LD50) of propoxur



(*) significant difference compared to control group (P < 0.05).

(**) highly significant difference compared to control group (P < 0.01).

Figure 7: Serum Creatinine in pigeon as affected by subchronic oral dosage (1/10 LD50) of propoxur



(*) significant difference compared to control group (P < 0.05).

(**) highly significant difference compared to control group (P < 0.

Figure 8: Serum Uric acid in pigeon as affected by subchronic oral dosage (1/10 LD50) of propoxur

4. DISCUSSION

A major function of the kidneys is a homeostatic mechanism involved in regulating electrolyte concentration, extracellular fluid (ECF) volume, osmolality, and acid–base balance. The kidney accomplishes these homeostatic functions both independently and in concert with other organs, especially the endocrine system. Endocrine hormones involved in coordinating these functions include renin, angiotensin II, aldosterone, antidiuretic hormone (ADH), and atrial natriuretic peptide (ANP) [20].

The sympathetic nervous system responds to changes in arterial blood pressure and blood volume by adjusting the glomerular filtration rate and the rate at which sodium is filtered from the blood. Sympathetic activity also regulate renal reabsorption of sodium and renin release. The renin-angiotensin-aldosterone system exerts its action through angiotensin II and aldosterone. Angiotensin II acts directly on renal tubule to increase sodium reabsorption. It also acts to constrict renal blood vessels, thereby decreasing the glomerular filtration rate and slowing renal blood flow so that less sodium is filtered and more is reabsorbed. Angiotensin II is also a powerful regulator of aldosterone, which acts to increase sodium reabsorption by the kidneys [21]. Stimulation of sympathetic nerve fibers to the kidneys, via β_2-adrenergic receptors on the granular cells, which leads to renin release and activate sodium retention processes [20]. The study of [22] approved that, intoxication of rats with carbamate leads to increase in norepinephrine and epinephrine which means that, these pesticides activate sympathetic system and potentiate sodium retention and this agree with our results in figure (1) which showed significant increase in sodium level in serum by suchronic intoxication with propoxur.

A variety of factors influence the distribution of K^+ between cells and ECF. A key factor is the Na^+/K^+-ATPase, which pumps K^+ into cells. If this enzyme is inhibited as a result of an inadequate tissue oxygen supply or digitalis overdose, for example, then hyperkalemia may result. In the present study, potassium level in serum was increased as a result of inhibitory effect of propoxur on erythropoiesis and iron absorption which leads to reduction of hemoglobin concentration and red blood cells count [23]. A decrease in ECF pH (an increase in ECF H^+) tends to produce a rise in ECF K^+. This results from an exchange of extracellular H^+ for intracellular K^+. When a mineral acid such as HCl is added to the ECF, a fall of 0.1 unit in blood pH leads to roughly a 0.6-mEq/L rise in plasma K^+ level. When an organic acid (which can penetrate cell membranes) is added, the rise in plasma K^+ level for a given fall in blood pH is considerably less. The fact that blood pH influences plasma K^+ level is sometimes used in the emergency treatment of hyperkalemia; intravenous infusion of a $NaHCO_3$ solution (which makes the blood more alkaline) causes H^+ to move out of cells and K^+, in exchange, to move into cells. In this study, significant decrease in HCO_3^- concentration and increase in PCO_2 leads to increase in H^+ concentration and acidemia, which potentiate our result of increase serum potassium level and disturbance of this electrolyte balance. Insulin promotes the uptake of K^+ by skeletal muscle and liver cells. This effect appears to be a result of stimulation of cell membrane Na^+/K^+-ATPase pumps. Hyperosmolality (e.g., resulting from hyperglycemia) tends to raise plasma K+ level; hyperosmolality causes cells to shrink and raises intracellular K^+ level, which then favors outward diffusion of K^+ into the ECF. The increase in blood glucose can be viewed as part of stress response triggered by Propoxur intoxication. The mechanism may be attributed to the stimulation produce by Propoxur to secrete epinephrine. This is because epinephrine has been reported to induce hyperglycemia due to its dual action on carbohydrate metabolism; it causes increased liver glycogenolysis and reduction in peripheral utilization of glucose [24]. Similar results were reported by Srivatava and Singh [25]were the treated fish elicited hyperglycemia and glycogenolysis in their blood when exposed to 5.20 and 2.608ppm of formothion and Propoxur for 8 days respectively. In another work by Srivatava and Singh [25] on the acute toxicity of Propoxur on carbohydrate metabolism of India catfish, *Heteropneustis fossilis*, showed a significant increase in blood pyruvate levels at 12 and 48hrs. Tissue trauma, infection, ischemia, hemolysis, and severe exercise release K^+ from cells and can cause significant hyperkalemia. This may be happen as a result of propoxur intoxication in the present study. An artifactual increase in plasma K^+ level, pseudohyperkalemia, results if blood has been mishandled and red cells have been injured and allowed to leak K+. Clearly, however, many factors affect the distribution of K^+ between cells and ECF, and so in many circumstances the plasma K^+ is not a good index of the amount of K^+ in the body.

Non-protein nitrogenous substances such as uric acid, urea and creatinine are increased only when renal function is below 30% of its original capacity in birds [26]. Plasma urea appears to be the single most useful variable for early detection of pre-renal causes of renal failure [26]. The elevation of serum urea concentration after a repeated oral doses (1/10 LD_{50}) administration of propoxur to pigeons shows an alteration in normal kidney function which might be related to the propoxur – induced renal dysfunction or may be due to heap to cellular disorder . A similar elevations in serum urea was observed with the chlorinated insecticide in rats [27], and with the carbamate insecticide in mice [28] and in rats [29]. In addition, Cerôn *et al*.[30] observed elevation of plasma urea level at 72 hours of exposure of eel (*Anguilla anguilla*) to a sub-lethal diazinon concentration of 0.042 mg/L. This suggests that probably proteins are being used to meet the increases energy demands during pesticides intoxication . Morever , the overall effect of glucocorticoids (secreted after a stressful stimuli) on metabolism will supply glucose to the organism by the transformation of proteins in the liver [31] . An accelerated rate of protein catabolism would result in an increase of amino

groups released from amino acids. These groups are converted firstly to uric acids, and secondly to urea in the detoxification process that takes place in liver [26]. Jayasree *et al.,* [30] recorded an increase in serum urea in day old male broiler chicks fed on deltamethrin (100 mg/kg feed) for 6 weeks, which may be due to the oxidative damage by free radicals. The elevation of serum urea and uric acid in the present study may be due to the decrease in the glomerular filtration rate induced by kidney dysfunction as a result of the action of propoxur. El-Missiry and Othman [23] reported that in-significant changes in blood urea nitrogen was observed after 1 hrs. and 7 days of treatment of rats with a subcutaneously injection with 3.3 mg / kg body weight with lannate . The present results showed significant increase in the serum uric acid after 6 and 9 doses of propoxur (1/10 LD_{50}). Similar observations were reported with pyrethroid insecticide in pigeons [29,33]and with the carbamate insecticides in rats [27]. Increase of blood urea in intoxicated groups of this study may be as a result of gastrointestinal bleeding and breaking down of blood cells by intestinal flora, which produce nitrogenous products and these were absorbed via hepatic portal vein to liver and finally were transformed into urea in blood [21].

Creatinine is the anhydrides of creatine (methyl -guanidinoacetic acid) and a constant constituent of normal human urine and is found in serum in a small amount [33, 34]. Jayasree *et al.*[26] recorded an increase in serum creatinine in day old male broiler chicks fed on deltamethrin (100 mg/kg feed) for 6 weeks, which may be due to the oxidative damage by free radicals. In the present study, repeated oral doses of propoxur administration to pigeons showed nonsignificant changes in serum creatinine. Similar observation was reported in rats treated with methomyl except for a slight, but significant, decrease after the 3rd week of methomyl treatment [33].

The decrease in HCO_3^- increase in PCO_2 indicated the presence of respiratory acidosis, which induced by treatment of pigeons with propoxur. This was also reported for rabbit [35] and for the gold skink [36]. In the present study pigeons treated with propoxur showed the respiratory acidosis i.e. increase in blood PCO_2 and decrease in blood pH that cannot be compensated. Also the disturbances in the kidney function (serum urea, uric acid and creatinine) may verify the decrease of the compensative activity of the kidney. Moreover, the decreases of HCO_3^- on long exposure to propoxur can be explained by continuous trans-epithelial elimination with the steady state production of non –volatile metabolic end products. In the present study, the observed respiratory acidosis may confirm the disturbances in blood gases transport mechanisms that may affected by hypoventilation and disturbances in pulmonary diffusing capacity under the effect of propoxur.

5. CONCLUSION

This study concluded that, intoxicated groups with propoxur showed significant increase in serum sodium, potassium, urea and uric acid, and significant decrease in venous blood bicarbonate, and non-significant changes in serum levels of calcium, phosphorus and creatinine as compared to control pigeons group.

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