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Effects of Chronic Exposure for Imidacloprid and Nano-Imidacloprid on some Biochemical and Hematological Parameters in Male Rats

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Abstract

Although considered a good alternative to organophosphate pesticides, there are reports indicating adverse effects of neonicotinoid insecticides on reproduction. The present work was designed to determine the chronic effects of orally administered for treated with 20 mg/kg/b.w. of imidacloprid pesticides and treated with 20 mg/kg/b.w. of nano-imidacloprid on biochemical blood profile in male rats for a duration of 60 d. Result: the exposure caused a significant decline in red blood cells (RBCs) and hemoglobin (H.b.) in all treated groups compared with the control, while causing an increase in blood platelets (PLT) and white blood cells (WBCs) in all rats treated as compared with the control rats. Furthermore, oxidative stress parameters showed a highly significant ($P \leq 0.05$) increase in malondialdehyde (MDA) after 60 d of exposure and a decline in reduced glutathione (GSH) and catalase activity (CAT). The imidacloprid pesticides and nano-imidacloprid lead to an increase the amount of total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL) in treated groups, while the high-density lipoprotein (HDL) level is reduced in treated groups as compared with the control group.

Keywords: Chronic, Imidacloprid, Nano-Imidacloprid, Biochemical, Hematological, Rats.

1. Introduction

Pesticides are the most effective means of pest control over the world. They improve the economic and social wellbeing of the population by increasing food production and the effective control of public health of vector-borne disease. Pesticides have played an essential part in trying to supply the increasing requirements of nutrition, cotton fiber, tobacco, etc., as well as for the prevention of vector-borne diseases. pesticides have been a crucial tool. The scientific community has turned its attention away from pesticide hazards and toward the creation of safer handling techniques (1). Pesticides were widely and randomly applied, and their resistance to physical, chemical, and metabolic breakdown led to their dispersion among the environmental foundations (2). Resulting to the emergence of various environmental and health difficulties caused by the increase of residue of chemical pesticides in environmental components as time passes, as well as the cases of poisoning and death and possible adverse effects on non-target

species and avian species through different mechanisms (3). In non-target species, pesticides can produce anything from minor pain to severe paralysis and death through binding to different enzymes, receptors, and other proteins, and the binding sites and adducts, along with residue of pesticides and their metabolites, can be used as biomarkers of exposure and effects. Neonicotinoids are a novel family of insecticides that have been proposed to attack the nervous systems of insects, causing paralysis and finally death (4). Imidacloprid (IMC) is a neonicotinoid insecticide that was the first of its kind to be approved for use. It is currently the insecticide with the fastest sales growth in the world and is being looked at as a potential replacement for the widely used organophosphorus pesticide diazinon, which is subject to phased revocation in many countries (5). (IMC) is a systemic insecticide that interacts with the nicotinic acetylcholine receptor, altering the transmission of synaptic information and resulting in systemic neurological disturbances. This chemical acts on the central nervous system of insects by obstructing the transmission of stimuli in the insect nervous system (6). Specifically, it causes a blockage of the nicotinergic neuronal pathway; imidacloprid prevents acetylcholine from transmitting impulses between nerves, resulting in the insect's paralysis and eventual death. It is effective on contact and via stomach action (7). Imidacloprid is a recently developed widespread pesticide that interacts with the chemical nicotine (the toxin in tobacco). The liver's biochemical and histological parameters serve as vital in finding out the harmful effects of various substances because of the liver's essential function in the metabolism and the removal of poisons from the body (8). The thyroid and liver are the main body parts affected by the lower-dose rate of imidacloprid during a longer-term, which results in a loss of weight. Imidacloprid has not been shown to be tumor-causing or mutagenic in routine laboratory tests on animals, but it has been shown to have cytotoxic effects on a variety of body parts, as evidenced by increased serum transaminase, glutamate dehydrogenase, and alkaline phosphatase functions, as well as changes in other physiologic parameters in rats and rabbits at low to medium dose rates (9). The utilization of biocompatible with biodegradable nanocarrier properties in formulating pesticides could ameliorate environmental protection. A recent study reported by (10) confirmed that a mixture of imidacloprid and lambda-cyhalothrin loaded with liposomes increased the potency and activity of insecticides. This study was aimed at evaluating the long-term effects of oral administration of imidacloprid insecticides and nano-imidacloprid (10 and 20 mg/kg/bw) for 60 days on the biochemical blood profile of male rats.

2. Materials and Methods

Chemicals and reagents: Imidacloprid (Yamador 20% SL), 1-(6-chloro-3-pyridylmethyl)-N-nitroimidazolidin-2-ylideneamine, is a product of Yamama Company and manufactured by Jordan. Preparation Nanoparticles: Nanoparticle preparation was performed in the College of Veterinary Medicine/University of AL-Qassim Green as described previously (11). Experimental design: The study used 21 healthy adult male rats from the College of Veterinary Medicine/University of AL-Qassim Green, weighing 250–300 g. The rats were mature at about three months old. Animals were kept alive under conditions of humidity (50-60%) and temperature (25-27) °C. The rats were divided into three equal groups after five days of acclimation. The first group was designated as the control group, the second group was administered 20 mg/kg/b.w. of imidacloprid, and the third group was administered 20 mg/kg/b.w. of nano-imidacloprid for 60 days.

2.1. Sample collection and analyses

After 60 days of treatment, fresh samples of blood were collected from all animals by heart puncture, which was used for evaluation of the complete blood count (CBC) and subjected to the extraction of serum. The serum samples were put in tubes at -20 °C for biochemical tests. Commercially available colorimetric kits Analytic on from The Biotechnologies Company, Sun Long Company The Eliza kit was used to measure serum levels of malondialdehyde (MDA), reduced glutathione (GSH), and catalase activity (CAT), in accordance with (12), (13), and commercially available colorimetric assays. Serum total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL) were measured using the methods described in (14), (15), (16), and (17).

2.2. Production of melanin pigment

To find the impact of various groups on study parameters, the statistical analysis system SPSS (2012) software was used. In this research, the Least Significant Difference (LSD) test was employed to evaluate means. The P value less than 0.05 is considered significant. Data are presented as mean ± standard deviation (S.D.).

3. Results

3.1. Hematological parameters

Rats treated to the imidacloprid at various doses for 60 days showed no signs of death. Several investigations in rats indicated that the imidacloprid may be able to cause a particular neurotoxicity (18). In this study, administration of pesticide for two months resulted in hematological variations with a significant decrease ($P<0.05$) in red blood cell count (RBC) and hemoglobin (H.b.) in rats treated with pesticide compared with the control group (**Table 1)**. This is in agreement with earlier results after intraperitoneal administration of pesticide (19, 20). Rats exposed to pesticides via ingesting had no apparent alteration in RBC and hemoglobin content, nevertheless. The result of RBC count was similar to results found by (21) who reported a significant decrease in RBC after treating pregnant female rats with bifenthrin. These results are in perfect agreement. With the study by (22), that showed a significant decline in hemoglobin levels and RBC counts and interpreted the decline in hemoglobin as the result of a rise in the amount of hemoglobin being oxidized. Additionally, a decreased amount of hemoglobin in line with RBC decrease may be due to pesticide-induced erythrocyte damage to membranes, which might result in hemolysis or harm to the blood's iron levels (23). Diminished H.b content can also be correlated to the reduction in the size of red blood cells or the impeded biosynthesis of Heme in bone marrow (24). RBC are particularly vulnerable to oxidative damage because of the significant amount of unsaturated lipids in their membranes and the greater cellular levels of oxygen and hemoglobin (25). The chemical (glutathione) that is recovered throughout the red blood cell and is responsible for protecting the cell from the effects of harmful chemicals may be inhibited by the impact of insecticides, which may also lead to increased lipid peroxidation brought on by oxidative damage and lower antioxidant enzyme activities in peripheral blood (26). Other explanations are reported by (27) that showed that any reduction in the number of RBC may be a result of a decrease in the amount of RBC manufacture in bone marrow or an increase rate of RBC destruction, in addition to rising red blood cell membrane fragility and changing membrane adaptation, which decreases the lifespan of circulating erythrocytes and raises the likelihood of hemolysis. However, when H.b. interacts with imidacloprid and

nanoimidacloprid pesticides, it produces a significant amount of free radicals that cause hemolysis and membrane lipid peroxidation (28). Hemolysis of blood cells can lead to a reduction in the number of erythrocytes that, in change, tends to be the factor linked to a decrease in hemoglobin amount, a reduction in H.b. amount, which may be associated with the decreased creation of the heme in bone marrow (29).

Table 1. Effect of Imidacloprid and Nano-Imidacloprid on hematological parameters of male rats for 60 days.

Group	Mean ±SE			
	RBC $10^{\wedge 12}.L^{-1}$	**WBC $10^{\wedge 9}L^{-1}$**	**PLT $10^{\wedge 9}.L^{-1}$**	**H.b $g.dl^{-1}$**
Control Group	5.83 ±0.34 A	5.25 ±0.30 B	209.11±12.0A	11.93 ± 0.69A
Treated with 20 mg/kg/ b. w. of imidacloprid	5.86 ± 0.34 A	5.62 ±032 B	217.02±12.53A	11.99 ±0.69 A
Treated with 20 mg/kg/ b. w. of nano-imidacloprid	4.94 ± 0.29 B	6.62 ±0.38 A	252.07±14.5A	9.98 ±0.58 B
LSD	0.477	0.521	20.289	0.998

Each value is a mean ± SE ; n=21; Statistical difference from the control: *significant at P≤0.05.

3.2. Oxidative stress biomarkers

Results of the current study revealed that chronic administration of imidacloprid and nano-imidacloprid led to oxidative stress in administered rats in contrast with control rats, as indicated by alterations in MDA, GSH, and CAT concentrations. The earlier findings concurred with Robinson *et al.* (35) who noticed that imidacloprid led to significant alterations in the levels of MAD, CAT, and GSH contents in the treated rats, as they indicated to be substantially higher in comparison to the controls, and GSH was significantly higher in the treated rat compared to the control group during 60 days. **Table 2** showed a significant ($p< 0.05$) reduction in CAT and GSH levels between every group receiving treatment to the reported mean value. (0.52±0.02, 0.34±0.02) and (55.39±2.86, 42.61±2.46) respectively compared with control group. Additionally, **Table 2** showed a significant ($p< 0.05$) rise in MDA levels in the blood of rats treated with imidacloprid and nano-imidacloprid after 60 days in the treat groups (1.91±0.13, 2.64±0.15) compared with the control group. This study's observation of an increase in MAD concentrations is in agreement with previous results (31). However, it has also been noted that these parameters decreased after ingesting and injecting insecticides intravenously, which is in agreement with Robinson (32). Increased concentrations of malondialdehyde (MDA) in imidacloprid and nano-imidacloprid rats receiving treatment may be caused by higher levels of reactive oxygen compound metabolites, particularly hydroxyl radicals, and change the antioxidant defense system (30). Imidacloprid and nano-imidacloprid treatment rats may lead to higher levels of oxidative stress through modifying the activity of enzymes in connection with antioxidant defense systems in the liver and kidney of male rats. Depending on the concentration, it reduced the levels of the antioxidant enzymes CAT and GSH by being able to eliminate free radicals; both enzymatic and non-enzymatic antioxidants work together to reduce the detrimental effects of ROS on tissues and is effective in preventing oxidative cell injury (33). Therefore, CAT is considered the greatest protection that defends cell macromolecules with structures with buildings from oxidative damage. Where on supplemental intake of multiple biochemical enzymes, Imidacloprid use in rats caused GSH concentrations to return to normal and a decrease in the histoarchitecture of the liver in Japanese quail (34).

Table 2. Effect of imidacloprid and nano-imidacloprid on oxidative stress parameters of male rats for 60 days.

Group	Mean ±SE		
	MDA nmol/ml	**CAT µmol/ml**	**GSH µmol/ml**
Control Group	1.75 ± 0.11 C	0.56 ± 0.03 A	57.42 ± 3.32 A
Treated with 20 mg/kg/ b. w. of imidacloprid	1.91 ± 0.11 C	0.52 ± 0.03 A	55.39 ± 3.2 A
Treated with 20 mg/kg/ b. w. of nano-imidacloprid	2.64 ± 0.15 A	0.34 ± 0.02 C	42.61 ± 2.46 C
LSD	0.174	0.043	4.579

Each value is a mean ± SE; n=21; Statistical difference from the control: *significant at P≤0.05.

3.3. Lipid profile biomarkers

Effect of Imidacloprid and Nano-Imidacloprid on lipid profile after 60 days of treatment showed highly significant ($p< 0.05$) The results in **Table 3** represent the increase in total concentration of total cholesterol, triglycerides, LDL and VLDL levels in all treated groups which values were (141.86±8.19, 174.25±10.01), (109.47±6.32, 137.95±7.96), (80.51±4.65, 119.5±6.91) and (21.89±1.26, 27.59±1.59) respectively as compared with control group. While the **Table 3** showed highly significant ($p< 0.05$) decrease, the level of HDL in all treated groups to recorded mean values (39.45±2.28, 27.15±1.57) respectively as compared with control group. Because imidacloprid metabolites accumulated in the liver, the main target organ for any method of detoxification, a considerable rise in cholesterol concentration level was seen (35). In all rat groups, there was a discernible rise in the serum triglyceride levels. The important factor is the production of free radicals that cause oxidative stress after taking imidacloprid, and this is taken into account for direct utilization of triglycerides and cholesterol as an antioxidant. The serum triglyceride levels significantly increased. The formation of free radicals that result in oxidative stress after taking imidacloprid is a significant issue, and this is taken into consideration for the direct usage of triglycerides and cholesterol as an antioxidant. This would ultimately result in the cessation of the free radical reaction and depletion of the triglycerides (TGs) during oxidative stress, as is evident from the considerable changes in hepatic biomarkers and associated abnormalities in the rats' histology and ultrastructure. Imidacloprid concentrations affected all treated groups cholesterol levels, LDL and HDL concentrations, and HDL levels when compared to control rats. These outcomes matched those that the FAO published in 1999. The histopathological abnormalities seen in this investigation were supported by alterations in oxidative stress, liver, and kidney biomarkers in rats exposed to imidacloprid and nano-imidacloprid. The liver exhibits significant degeneration, infiltration, inflammation, and localized hepatic bleeding according to histological studies. Severe necrosis, inflammation, glomerular tuft atrophy, vacuolation, and localized bleeding were seen in the kidney.

Table 3. Effect of Imidacloprid and Nano-Imidacloprid on lipid profile of male albino rats given daily oral doses for 60 days.

Group	Mean ±SE				
	T.C mg/dl	TG mg/dl	HDL mg/dl	LDL mg/dl	VLDL mg/dl
Control Group	132.78±7.67B	99.25± 5.73C	43.07± 2.49A	69.86 ±4.03 D	19.85 ±1.15 C
Treated with 20 mg/kg/ b. w. of imidacloprid	141.86±8.19 B	109.47±6.32C	39.45±2.28 B	80.5 ± 4.65 C	21.89 ±1.26 C
Treated with 20 mg/kg/ b. w. of nano-imidacloprid	174.25±10.01A	137.95±7.96A	27.15±1.57D	119.5±6.91A	27.59 ±1.59 A
LSD	13.389	10.459	3.212	8.268	2.083

Each value is a mean ± SE; n=21; Statistical difference from the control: *significant at P≤0.05.

4. Conclusion

The findings of this study demonstrate that chronic exposure to imidacloprid and nano-imidacloprid induces significant hematological, oxidative stress, and lipid profile alterations in male rats. The decrease in red blood cells and hemoglobin, along with increased white blood cells and platelets, suggests the pesticides may interfere with normal blood function. Higher oxidative stress markers (MDA) and lower antioxidant levels (GSH, CAT) indicate significant cell damage. Furthermore, the rise in cholesterol, triglycerides, and LDL, with a drop in HDL, revealed potential risks for metabolic and cardiovascular health. Given these findings, the widespread use of these pesticides should be reconsidered, particularly in environments with high human and animal exposure.

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Conflict of Interest

The authors declare that they have no conflicts of interest.

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Ethical Clearance

All experimental rats were kept in accordance with national and international legislation and research protocols established by the Ethics Committee on Animals, Guide for the Care and Use of Laboratory Animals" of the University of Baghdad, College of Science, Department of Biology **(**No. 984 A.P. on March 14, 2022**)**

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