Journal of Applied Veterinary Sciences, 7 (4): 88-93 (October, 2022)
ISSN: Online: 2090-3308, Print: 1687-4072
Journal homepage : https://javs.journals.ekb.eg

Identification of Histopathological Changes Induced by Amitraz in Rats

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ABSTRACT

Amitraz is used worldwide as a pesticide. It produces toxic effects when misused. The present study examined the histopathological changes of Amitraz in the hepatocyte and kidney tissues of laboratory albino rats. Thirty-six albino rats were used and they were randomly divided into six groups. Amitraz was given through oral gavage at different doses as follows: The control group (group one) received 5ml/kg of normal saline, group two received 100mg/kg, group three had 250mg/kg, group four received 500mg/kg , organs extraction from the rats (livers and kidneys) were performed after three hours from giving amitraz administration in groups one, two, three, and four. Group five received 500mg/kg and had organ collection after 5 hours of administration; group six received the same as the last dose and had organ collection after 24 hours of administration. The results revealed that Amitraz produced severe histopathological effects on the liver and kidney tissues compared to the control group. The changes were obvious in rats treated with high-dose groups. Severe and significant histopathological changes were evident in the hepatocyte and kidney tissues in group six of the treated rats compared to groups 5 and 4. While the lowest given dose group showed normal tissues, indicating that Amitraz requires a larger quantity to produce the histopathological action. The study concluded that Amitraz has hepatotoxic and nephrotoxic effects when an overdose is used.

Keywords: Amitraz, Hepatotoxicity, Histopathology, Nephrotoxicity, Rats.

Original Article:
DOI:HTTPS://DX.DOI.ORG/10.21608/JAVS.2022.154375.1169
Received :04 August, 2022.
Accepted :10 September, 2022.
Published in October, 2022

J. Appl. Vet. Sci., 7(4): 88-93.

INTRODUCTION

Amitraz is a dimethyl formamidine chemical substance (N- 2, 4-(dimethyl phenyl) -N-[2 , 4-dimethylphenyl imino]-N-methylmethanimidamide and it is used worldwide as an insecticide/acaricide against many pests of animals and plants **(Filazi *et al.*, 2004; Vucinic *et al.*, 2007).** Amitraz is from the formamidine family. It is considered the most effective and efficient substance in its family and is used at low cost in veterinary, pharmaceutic, agriculture, and horticulture fields **(Gupta, 2012).** The primary use of Amitraz is against Varroa disease, which is caused by a mite called Varroa destructor; the varroa disease produces considerable damage to the beehives and leads to bee death **(Mullin *et al.*, 2010).** Amitraz shows the different mechanisms in animals and insects. In animals, it acts on the alpha 2 (α_2) - adrenergic receptors in the central nervous system (CNS), causing hyperstimulation of the receptor by suppressing the release of catecholamine as well as by inhibiting the monoamine oxidase enzyme **(Gupta, 2012).** In insects, Amitraz stimulates octopamine receptors and causes convulsion, eventually leading to the insect's death.

There are many formulations of Amitraz. Amitraz's commercial formulation usually consists of 12.5% - 20% of the drug in its organic solvents, especially 75% xylene **(Tarallo *et al.*, 2009).** The main routes of amitraz exposure are ingestion by oral route, inhalation and dermal routes, causing toxicities in humans and animals **(Krieger, 2010; Wilson and Murty, 2018).** The toxic clinical signs of amitraz poisoning are CNS depression, deep coma, bradycardia, sedation, hyperglycemia, mydriasis,

delayed gastrointestinal transit, and other symptoms observed in animals and humans **(Shilpakar *et al*., 2020).** The lipophilic property of Amitraz gives it rapid absorption in the acidic media of the stomach **(Shimshoni *et al*., 2019).** The highest peak in plasma level detection was after two hours of oral administration. At the same time, the maximum tissue level of Amitraz is evident in the bile, intestine, liver, kidney, eye, and muscle tissues **(Nanjundappa *et al*., 2021).** Urine levels peak following 6 to 23 hours of amitraz ingestion in canines **(Epstein *et al*., 2021).**

The fundamental treatment for amitraz poisoning is a quick diagnosis. The diagnosis of Amitraz is by identifying the nature of the ingested pesticide. Amitraz shares the organophosphorus insecticide poisoning signs; they produce the same characteristic features that make the diagnosis challenging **(Mustafa and Al-Baggou, 2020).** The presence of hypothermia, bradycardia and hyperglycemia, in the absence of secretory states, are all critical points for amitraz diagnosis in case of poisoning and are used for differentiating it from other poisonings. Furthermore, both atipamezole and yohimbine have been used to treat amitraz intoxication **(Kizil *et al*., 2008).** The study aimed to investigate the hepatotoxic and nephrotoxic changes in the tissues caused by the given oral Amitraz in rats at different doses.

MATERIALS AND METHODS

1. Laboratory animals

Thirty-six adult albino rats of both sexes weighing (150-300 g b. wt) were used. The rats were obtained from an animal house in the College of Veterinary Medicine, Duhok University. The laboratory animals were housed under standard conditions with a housing temperature (18 - 24ºC) and 10/14 hours of the light/dark cycle. In addition, water and food were given ad Libitum to them. Before the experiments, the animals were permitted to enter the new environment for half an hour. The ethics committee of Veterinary Medicine College at the University of Duhok approved the current study.

2. Experimental design

Animals were randomly divided into six groups, each of 6 rats. All groups were given Amitraz manufactured by Jordanian company VAPCOZIN at 12.5% concentration. All doses depended on a pilot study on adult female and male rats. Amitraz was given once by oral gavage and the groups of animals were categorized as follows:

Group 1: Control group was treated with 5ml/kg of normal saline.

Group 2: Rats received Amitraz at a dose (100mg/kg b.wt). Organ collection was performed after 3 hours.

Group 3: Rats were given Amitraz at a dose (250mg/kg). Then, organ collection was performed after 3 hours of administration.

Group 4: Rats received Amitraz at a dose (500mg/kg) and had organ collection after 3 hours of administration.

Group 5: Rats were treated with Amitraz at a dose (500mg/kg) and after 5 hours from administration, the organs were extracted from them.

Group 6: Rats were administered Amitraz at a dose (500mg/kg) and after 24 hours of administration, the organs were obtained from the rats.

3. Sample collection

Laboratory animals were euthanized with diethyl ether inhalation **(Aguwa *et al*., 2020).** The collected organs were livers and kidney tissues in all groups. After that, the tissue samples (0.5 cm in size) were obtained from both organs and fixed in 10 % neutral buffer formalin. The histopathological procedure was applied to prepare the tissue sections **(Luna, 1968)**. The organ samples were dehydrated with ascending grades of ethanol (70%, 80, 90%, and 100% I and 100% II). After that, the clearing process was produced using xylene and eventually embedded in paraffin wax at a melting point (56-68 ºc). Thin tissue sections of 4-5 µm in thickness were equipped using Rotatory Microtome (Leica, Germany) and stained with Harris Hematoxylin and Eosin (H&E). Then all the prepared slides were analyzed using an optic microscope with a Digital camera Leica, Germany.

RESULTS

3.1. Histopathological findings

The liver section of control rats displayed the typical histological structure of portal vein and hepatic lobs without any modifications in the tissue structure (Fig. 1).

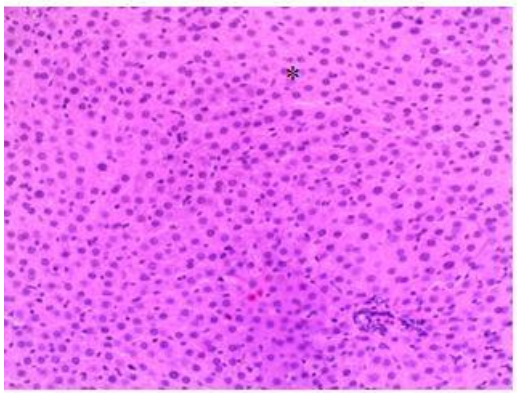

Fig. 1: The microscopical appearance of normal rat liver showing a typical structure of the liver (black asterisk). H&E, 400 X.

3.2. Histopathological findings of induced Amitraz on the liver

Amitraz showed different changes in the liver of the experimented rats. The rats in group 6 with amitraz dose at 500mg/kg after 24 hours of administration showed per-portal infiltration of Inflammatory cells around the portal artery (Fig. 2-a). Also, the changes in (Fig.2-b) of the mentioned group showed severe fatty changes in hepatocytes with the proliferation of kupffer cells.

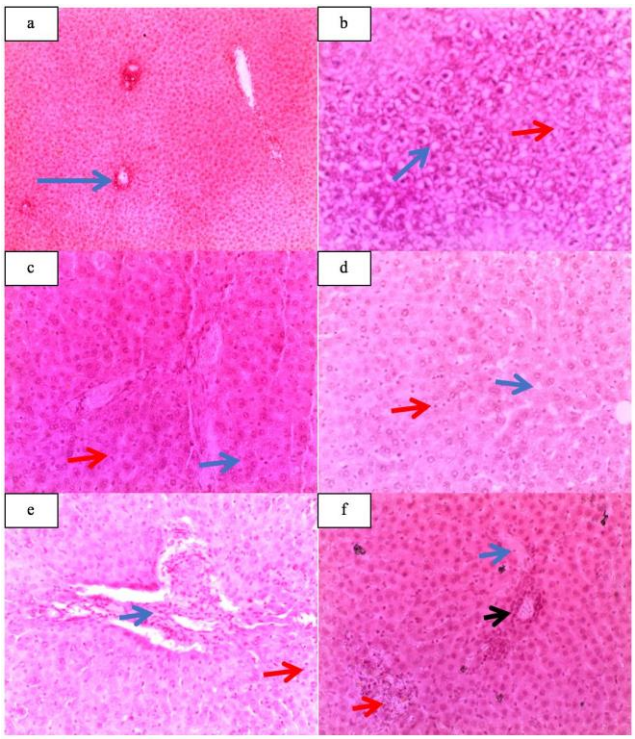

Fig. 2: Histopathological examination of rat liver(a-h): (a&b) group 6 of rats given 500mg/kg, (a) the liver shows peri-portal infiltration of Inflammatory cells around portal artery blue arrow (b) shows severe fatty changes of hepatocytes blue arrow, the proliferation of kupffer cells red arrow (c). Group 5 at 500 mg/kg shows mild degenerative changes of hepatocyte blue arrow and proliferation of kupffer cells red arrow. Group 4 at 500 mg/kg, (d) showing focal area degenerative changes of hepatocytes blue arrow and moderate proliferation of kupffer cells red arrow in (e) showing focal aggregation of inflammatory cells around the portal artery blue arrow and moderate proliferation of kupffer cells red arrow. Group 3 at 250mg/kg, showing mild focal degenerative changes of hepatocytes blue arrow, focal area of hepatitis red arrow with infiltration of inflammatory cells around of portal artery black arrow (f) H&E, 400X.

In group 5, after 5 hours of 500mg/kg of amitraz administration, exhibited degenerative changes in hepatocytes (Fig. 2-c). The rats in group 4, with amitraz dose of 500mg/kg and after 3 hours of administration, showed a focal area of degenerative changes of hepatocytes, a moderate proliferation of kupffer cells, and focal aggregation of inflammatory cells around the portal artery (Fig. 2-d & 2-e).

Group 3 of rats were given oral Amitraz at 250mg/kg; after 3 hours of administration, the histopathological findings were milder than the previous groups. Mild degenerative changes of hepatocytes, focal area of hepatitis with infiltration of inflammatory cells around the portal artery, and portal vein congestion were detected (Fig.2-f & 3-a).

Ultimately, very mild alterations were observed in group 2. In this group, the rats were administered the lowest dose of Amitraz among all groups at 100mg/kg. After 3 hours of administration, slight degenerative modifications of hepatocytes were identified in the liver (Fig. 3-b).

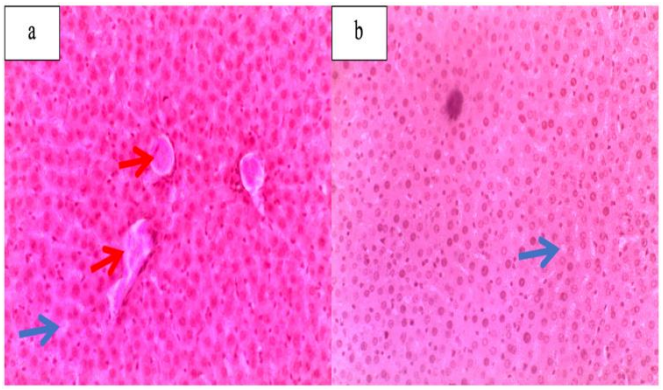

Fig. 3: Histopathological examination of rat liver (a-b): group 3 at 250mg/kg shows mild degenerative changes of hepatocytes blue arrow, congestion of portal vein red arrow shows in (a). Group 2 at 100mg/kg, showing mild degenerative changes of hepatocytes (fatty changes) blue arrow (b). H&E, 400X.

3.3. Histopathological findings of induced Amitraz on the kidney

The kidney section of control rats exhibited the standard histological structure of glomeruli and renal tubules without any modifications in the form of the tissue (Fig. 4). The kidneys of the tested rats also had their fair share of histopathological effects compared with the control group.

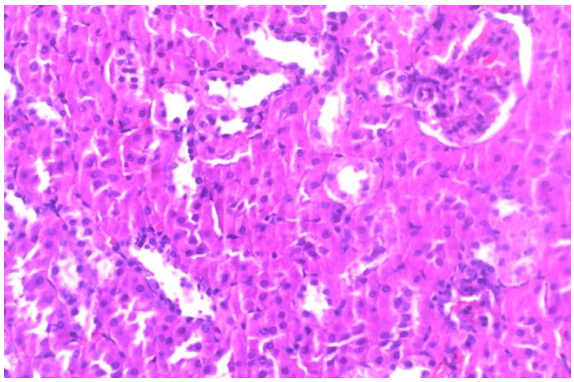

Fig. 4: The microscopical appearance of a normal rat kidney shows the kidney's typical structure (black asterisk). H&E, 400 X.

The changes in (Fig. 5 a and b) demonstrate that after 24 hours of amitraz administration at a dose of 500mg/kg in group 6 had shown severe degenerative changes in renal tubules, most of the renal tubules were swelled. And it displayed severe inflammatory alterations of glomeruli and narrowing of bowman's space indicating glomerular hypertrophy.

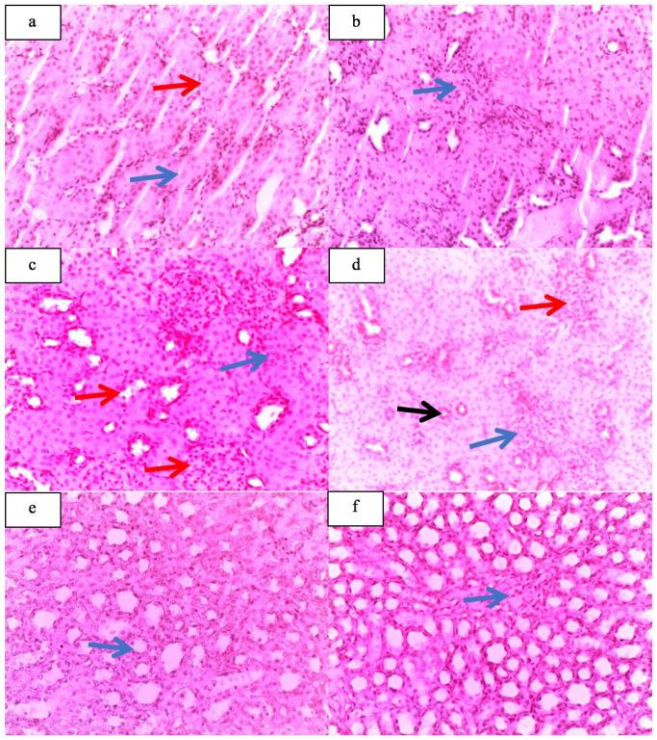

Fig. 5: Histopathological examination of the rat kidney (a-f). (a & b) group 6 of rats with 500 mg/kg, (a) showing severe degenerative changes of renal tubules blue arrow, swelling of cells lining of renal tubules red arrow and (b) showing severe inflammatory changes of glomeruli as narrowing of bowman's space indicating glomerular hypertrophy blue arrow. Group 5 at 500 mg/kg, showing moderate infiltration of inflammatory cells of the interstitial tissues blue arrow and moderate degenerative changes of tubules and glomeruli red arrow (c). Group 4 at 500 mg/kg, showing diffuse glomerulitis blue arrow, interstitial nephritis, red arrow and atrophy of some of the tubules, the black arrow (d). Group 3 at 250mg/kg, showing mild degenerative changes of most renal tubules blue arrow(e). Group 2 at 100mg/kg, showing most renal tubules appear normal structure and mild thickening of intestinal tissue, a blue arrow(f). H&E, 400 X.

Similarly, the rats in group 5, with amitraz treatment at a dose of 500mg/kg, showed moderate infiltration of inflammatory cells of the interstitial tissues and mild degenerative changes of tubules and glomeruli. These changes were observed after 5 hours of amitraz administration (Fig. 5-c).

Groups 5 and 6, who administered a dose of 500 mg/kg of Amitraz in group 4, revealed diffuse glomerulitis, interstitial nephritis, and some glomeruli necrosis. These observations were evident after three hours of amitraz treatment (Fig. 5-d). However, three hours of amitraz treatment with a dose of 250 mg/kg in group 2 showed mild degenerative changes in renal tubules and glomeruli, as demonstrated in (Fig. 5-e). Finally, after three hours of giving the lowest dose of amitraz treatment to group 2, it showed almost normal renal tissue structures. Most renal tubules were typical for this group of rats administered 100mg/kg (Fig. 5-f).

DISCUSSION

The present study investigated the histopathological effect of Amitraz against induced nephrotoxicity and hepatotoxicity in rats. Several studies have been conveyed to clarify the mechanism of amitraz toxicity to the liver and kidney with only a few researches being performed on the histopathology of amitraz insecticide.

In animals, Amitraz works as the alpha 2-adrenergic agonist agent, similar to clonidine **(Iken *et al*., 2020).** Amitraz intoxication can be mistaken for carbamate or organophosphate poisoning because all three show numerous parallel clinical signs **(Dhooria *et al*., 2015).** The acute median lethal dose (LD_{50}) of oral Amitraz in the chick is 53.05 mg/kg of body weight **(Al-Hammdani and Al-Baggou, 2014)**; in mice is > 1600 mg/**kg (Al-Thani *et al*., 2003)** and in rats is > 700 mg/kg **(Mahmood and Mohammed, 2019).**

Amitraz is well absorbed through oral administration owing to its high lipophilic property; that is how it marks a possibly hazardous agent for humans and animals. The pharmacokinetics of Amitraz in various species have demonstrated that nearly 53% to 80% of Amitraz is emitted in the urine when the agent is conveyed orally in dogs, mice, rats, and humans within a day **(Epstein *et al*., 2021).** The maximum residue concentrations were seen in the liver and kidney tissues. Its levels rapidly decreased afterward. This was measured in the first two hours after the oral delivery in mice and rats **(Marafon *et al*., 2010; Filazi and Yurdakok-Dikmen, 2018)**. It is reported that conversion of Amitraz to an extra toxic substance known as mono-N-methyl derivative in the gastrointestinal system after oral administration is very rapid. The liver metabolizes this substance, mainly to 4-amino-3-benzoic acid, which is not toxic and is eventually excreted by urine and bile. When the liver is exposed to these by-product metabolites, it cannot detoxify it, causing disturbances **(EFSA, 2016).**

In the current study, several pathological changes were observed in the livers and kidneys of rats exposed to commercial Amitraz. However, as the dose was proportionally less, the severity of histopathological changes was also less observed.

Our research parallels a former study that revealed the liver sections of the control group of rats

showed typical structures. Whereas the liver of treated groups spotted severe pathological findings, and the severity was different among the groups of study when compared to the control group. The histopathological findings were similar to previous work **(Filazi *et al*., 2004).** The hepatocyte degeneration and liver tissue structural changes were marked and detected considerably in the treated liver.

The current work in amitraz-treated groups of rats showed progressive destruction of liver tissue. The liver showed severe pathological changes at the highest dose after one day from treatment and this agrees with a previous histopathological study showing a similar detection **(Omoja *et al*., 2016).** The hepatotoxicity and liver damage due to only one oral dose of amitraz administration indicated the toxic effects of the pesticide. Interestingly, Amitraz can exert its poisonous action short after taking the insecticide, which was detected in the current work, in which three to five hours of post-administration were enough for the pesticide to produce histopathological effects. Amitraz's poisonous actions are bradycardia, hypotension, dullness, loss of appetite, gastrointestinal stasis, and central nervous system depression **(EFSA, 2016).** Thus, lesions in the kidneys and the livers resulted in hydropic degeneration and fatty changes in the hepatocytes and these are common changes from toxic material intake **(Al-Thani *et al*., 2003).**

Moreover, the current result revealed that the lowest dose of Amitraz showed nearly normal liver and kidney histological tissues compared with the control group. These findings are concurrent with the former author **(Filazi *et al*., 2004).** Administration of growing doses of Amitraz exhibited histopathological changes in the kidney and liver of treated rats. Severe degenerative hepatic changes, hydropic degeneration, and hydropic and fatty degenerative injuries were seen in animals who received the commercial amitraz formulation at a dose equal to or higher than 250 mg/kg. This formulation of Amitraz guided the development of epithelial cell necrosis at a dose of 500 mg/kg **(Filazi *et al*., 2004; Vucinic *et al*., 2007)**.

CONCLUSION

The current study found that Amitraz produced severe histopathological changes in the livers and kidneys of the treated rats. The histopathological changes were dramatically found in groups of treated rats with high doses compared to the control group. Conversely, the lowest dose group of Amitraz has no significant effects indicating that Amitraz requires a larger quantity of the drug to produce the histopathological actions.

ACKNOWLEDGEMENT

We appreciate the contribution of Dr. Mahdi Ali, Assistant Professor of Molecular Pathology and human biology, College of Veterinary Medicine, Duhok University, for his generous assistance in setting up the histopathological study.

Conflict of interest

The authors acknowledge that there is no conflict of interest regarding the research idea and tools, actual, potential and financial, directly or indirectly.

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How to cite this article:
Zainab Taha Mohammed, Rizgar Khalid Nabi, Yaareb Jaafar Mousa, and Mahmood Basher Mahmood, 2022. Identification of Histopathological Changes Induced by Amitraz in Rats. Journal of Applied Veterinary Sciences, 7 (4): 87– 93.
DOI: **HTTPS://DX.DOI.ORG/10.21608/JAVS.2022.154375.1169**