Biochemical Effects of Deltamethrin on Inflammatory Markers and Iron Homeostasis

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A B S T R A C T

A total number of 80 Wister male rats, 9 -wk. old were taken, weighed and divided into four experimental groups to evaluate the oral toxicity induced by Deltamethrin (DLM) administration (0.87, 8.7 and 17.4 mg/kg B.W) for a period of 9 weeks on Iron homeostasis and inflammatory markers of Wister male rats. The results indicated that DLM was associated with a statistically significant elevated in levels of Interluken2(IL2), Interluken6(IL6), Histamine, cortisol, Ammonia, Haptoglobulin, Transferrin and total iron binding capacity (TIBC), while decreased in Iron (Fe) and Ferritin levels was recorded. These results indicated that DLM is a toxic pyrethroid pesticide that produced significant Alteration in Iron Homeostasis and inflammatory markers.

(Key word: DLM, Iron Homeostasis, inflammation)

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1. INTRODUCTION:

Deltamethrin (DTM) is a synthetic type II pyrethroid insecticide highly used by farmers and home users. This pesticide has lipophilic properties that facilitate a high absorption and can cause toxicity in non-target organisms *(*Oliveiraa *et al.*, 2018*)*. Insecticide holds a unique position among environmental contaminants being present in the environment in such small quantities as compared to other contaminants such as industrial wastes and fertilizers. The major factors which account for public and scientific concern is their biological activity (Hamid *et al*., 2012). Although deltamethrin is initially thought to be least toxic, a number of recent reports showed its toxicity in mammalian and non-mammalian laboratory and wildlife animal species. The article sheds light on deltamethrin induced various toxicities during acute and chronic exposure in different species (Hasibur *et al.*, 2014).

According to some reports, the liver was found to accumulate many metabolites since it is the principle site of DLM metabolism, and the kidneys are considered as the main excretory organ in mice and rats (Abdel-Daim *et al.*, 2015). Moreover, Exposure to DLM may leads to hepatotoxic, nephrotoxic and neurotoxic side effects for human and many species, including birds and fish (Abdel-Daim *et al.*, 2016). Members of pyrethroid family also exert their toxic effects through induction of oxidative stress, traces of this are evident in several organs, tissues, and cells, such as liver, brain, kidney (Gunduz et al., 2015). These reports suggested that excessive ROS and subsequent oxidative stress may play important role in DLM induced manifestations however the detailed mechanism is remain resolved. Therefore, the objective of this study aimed to identify and characterize the inflammatory markers and

iron hemostasis profile which are responsive to DLM and its elicited pathogenesis.

2. MATERIALS AND METHODS:

This study was carried out at Institute of Medical Entomology. Eighty Wister male rats, 9 -wks-old were taken, weighed and randomly distributed into four experimental groups. Rats were housed in separate metal cages, then the four experimental groups were arranged as, the first as a control group (un-treated) given corn oil as vehicle orally, the second group orally administrated with DLM at dose of 0.87 mg/kg body weight (1/100th LD50), the third group orally administrated with DLM at dose of 8.7 mg/kg body weight (1/10th LD50), the fourth group orally administrated with DLM at dose of 17.4 mg/kg body weight (1/5th LD50). All the groups were treated for 9 weeks and at the end of experiment, animals were weighed and sacrificed using light ether anesthesia, to studying their effects on some sera contents such as IL2, IL6, Histamine, cortisol, Ammonia, Haptoglobulin, Transferrin, total TIBC, Fe and Ferritin.

The weights of the animals in each treatment group were determined (ScoutPro SPU601, Ohaus) once every week and this was used to calculate the amount of pesticide administered as shown in Eq. 1.

X mg of pesticide=Group dose × Kg body weight of animals (1)

X mg of the pesticide was orally administrated, at 48 hour intervals and fed to the rats. Deltamethrin is a synthetic pyrethroid insecticide (C22H19Br2NO3) (98.1% purity) were obtained from Kafr EL Zayat co.

Data collection and estimated parameters:

After Experiment period, blood samples were collected via direct heart puncture in centrifugation tubes from without anticoagulant and kept at room temperature for one hour to clot. The samples were centrifuged at 5000 rpm for 15 minutes to separate clear serum. After that IL2 (according to manufacture), IL6(according to manufacture), Histamine (Hermann et al., 1994), cortisol (Mullner *et al.,* 1991), Ammonia (Neeley and philipson, 1988), Haptoglobulin (Johnson et al., 1999), Transferrin (Hellsing, 1973), TIBC (Nisssen, 1972)., Fe (stookey, 1978) and Ferritin (Valberg, 1980) were determined using available commercial Kits.

Statistical analysis: Using computer software SPSS version 22.0, simple one way ANOVA was used to study the effect of Deltamethrin on each parameter at different doses and Duncan's multiple range tests was used to differentiate between significant means (Snedecor, 1989). The recorded data of rates was analyzed using two-sided Fisher's exact test, and $P < .05$ was considered as statistically significant.

3. RESULTS:

Significant reductions in Fe level were observed in DLM treatment groups (0.87, 8.7 and 17.4 mg/kg B.W) when compared with normal control group, lowest mean value was observed in (17.4 mg/kg B.W) DLM treated animals (Table 1). Also, animals of both low dose and high doses Deltamethrin treated groups (0.87, 8.7 and 17.4 mg/kg B.W) after 9 weeks revealed a significant decline in Ferritin levels as compared to control group, with lowest mean value in (17.4 mg/kg B.W) DLM treated animals (Table 1). On other hand, significant elevation trend in serum Transferrin after 9 weeks treatment in low dose and high doses Deltamethrin treated groups (0.87, 8.7 and 17.4 mg/kg B.W) as compared to control group (Table 1). In addition, TIBC level also revealed significant increases in a dose dependent manner in

DLM treated groups (0.87, 8.7 and 17.4 mg/kg B.W) after 9 weeks respectively as compared to control group (Table 1). Furthermore, animals of both low dose and high doses Deltamethrin treated groups (0.87, 8.7 and 17.4 mg/kg B.W) after 9 weeks showed a significant elevation in Haptoglobin levels in a dose dependent manner as compared to control group (Table 1).

IL2 level show significant increase ($P < 0.001$) in low dose and high doses Deltamethrin treated groups (0.87, 8.7 and 17.4 mg/kg B.W) after 9 weeks as compared to control group, with highest mean value in (17.4 mg/kg B.W) DLM treated animals (Table 1). Also, animals of both low dose and high doses Deltamethrin treated groups (0.87, 8.7 and 17.4 mg/kg B.W) after 9 weeks revealed a significant elevation ($P < .001$) in IL6 levels in a dose dependent manner as compared to control group (Table 1).

On other hand, significant elevation trend ($P > 0.001$) in serum Cortisol after 9 weeks treatment in low dose and high doses Deltamethrin treated groups (0.87, 8.7 and 17.4 mg/kg B.W) in a dose dependent manner as compared to control group (Table 1). Additionally, Serum Histamine level revealed significant increases ($P < 0.001$) in low dose and high doses Deltamethrin treated groups (0.87, 8.7 and 17.4 mg/kg B.W) after 9 weeks in a dose dependent manner as compared to control group (Table 1). Furthermore, animals of both low dose and high doses Deltamethrin treated groups (Group II, Group III and Group IV) after 9 weeks showed a significant elevation ($P < 0.001$) in serum Ammonia levels as compared to control group (Table 1) with highest mean value in (17.4 mg/kg B.W

Table 1: Effect of DLM treatment on Iron Homeostasis and inflammatory markers.

Parameters	Control (-ve)	DLM , mg/kg B.W	DLM , mg/kg B.W	DLM , mg/kg B.W	Sig.
		0.87	8.7	17.4	
Fe	143.81 ± 4.51 [a]	135.91 ± 5.71 [ab]	126.94 ± 2.38 [b]	109.10 ± 6.84 [c]	.003
Ferritin	27.66 ± 1.43[a]	25.27 ± 2.17[a]	23.27 ± 2.38[a]	16.57 ± 1.2[b]	.007
Transferrin	184.08 ± 6.2[a]	193.41 ± 3.35[b]	199.38 ± 6.04 [b]	37.25± 0.85[d]	.005
Haptoglobin	40.67 ± 2.17 [c]	46.33 ± 5.74 [c]	61.22 ± 2.46 [b]	87.98 ± 4.91 [a]	0.001
TIBC	330.52 ± 5.02 [c]	367.24 ± 1.19 [b]	412.00 ± 1.34 [a]	443.75 ± 12.03 [a]	0.001
IL2	0.31 ± 0.03 [b]	0.38 ± 0.04 [b]	0.49 ± 0.07 [b]	1.02 ± 0.10 [a]	0.03
IL6	5.02 ± 0.41 [c]	5.42 ± 0.33 [bc]	7.87 ± 0.71 [b]	11.41 ± 1.39 [a]	0.001
Histamine	1.78 ± 0.16 [c]	3.40 ± 0.67 [c]	9.96 ± 0.84 [b]	17.99 ± 2.27 [a]	0.001
Cortisol	5.38 ± 0.48 [c]	13.38 ± 1.02 [c]	23.30 ± 3.41 [b]	41.36 ± 4.60 [a]	0.001
Ammonia	26.20 ± 2.01 [c]	45.30 ± 3.13 [b]	57.05 ± 3.76 [b]	88.61 ± 5.64 [a]	0.001

Data are presented as (Mean ± S.E). S.E = Standard error.

Mean values with different superscript letters in the same row are significantly different at ($P<0.05$).

4. DISCUSSION:

The Present study has mainly aimed to identify and characterize the inflammatory markers, stress indicators and iron hemostasis profile which are responsive to DLM and its elicited pathogenesis. The obtained data showed significant Alteration in the mean value of serum IL2, IL6, Ammonia, Cortisol, transferrin, Haptoglobin, TIBC, Histamine, Iron and Ferritin in DLM treated groups in a dose dependent manner. The presented results were in agreement with the data reported by (Arora *et al.,* 2016) who stated that, The protein level of diverse cytokines was up-regulated in DLM treated group. confirmed that DLM was able to induce an inflammatory response in animals; In addition, it was also observed that a dose-dependent increase in ROS and altered enzymatic antioxidant defense in the liver of DLM treated rats. Oxidative damage from free radical trigger inflammation via a cytokine mediated immune response. Which involve releasing of anti-inflammatory and pro-inflammatory cytokines (Mani *et al.,* 2017).Furthermore, (Heneka and O'Banion, 2007) revealed that DLM cause direct cellular damage, oxidative stress and free radicals that activate the transcription of multiple inflammatory genes.

Many results demonstrated the relation between inflammatory cytokines and oxidative stress. Elevated pro-inflammatory cytokine levels are correlated with oxidative stress through generation of ROS and other inflammatory mediators by immune cells (Guerri and Pascual, 2010). Accordingly, oxidative stress and inflammation often occur in tandem in many diseases and disorders, including pesticide exposure (Enciu et al., 2013).These suggestion were agreed with (Maalej *et al.,* 2017) who stated that the inflammatory disorder might be due to the up-regulation of cyclooxygenase-2 (cox-2), thus playing a key role in promoting inflammation. In this respect, it was recorded that, Inflammation is considered as one of the main mechanisms for the deltamethrin toxicity (khalatbary et al., 2016). Other studies reported that deltamethrin significantly increased the tumor necrosis factor (TNF- α) and caused degenerative changes in kidney tissue after oral administration (Abdel-Daim *et al.,* 2016). Moreover, the administration of deltamethrin considerably increased the expression ofcyclooxygenase-2 (cox-2) (khalatbary *et al.,* 2016). Additionally, (Shen *et al.,* 2015) concluded that the elevated oxidative stress and DNA oxidative damage is the key responsive elements of DLM elicited toxicity. The increased expression of inflammatory markers and cytokines was found to be associated with DLM exposure which indicated the inflammation inducing property of DLM (Ogaly *et al.,* 2015).

Furthermore (Isaac, 2008) who showed that, plasma haptoglobin concentration was increased several folds in the event of an inflammatory stimulus such as infection, injuiry or malignancy. IL-6, produced through the activities of the primary cytokines TNF-α and IL-1, is the major inducer of the expression of the protein. Also (Ramzy *et al.,* 2014) revealed that, serum cortisol levels showed a significant increasing during acute and chronic exposure to pesticides. The elevation of cortisol because of pesticides exposure was widely used as a primary response to stressors caused by pesticides. Additionally, (Hamidipoor et al., 2014) demonstrate that, long-term exposure to deltamethrin is probably associated with the increased biosynthesis of cortisol. Iron deficiency is common and has certain mechanisms involved in its pathogenesis mainly a state of subclinical inflammation. The low iron levels are most probably caused

by the inflammatory mechanisms (Khan *et al.*, 2016). Other researchers had identified a novel finding of pyrethroids in altering cellular iron homeostasis without imparing cell viability. SUN *et al.*, (2014) have demonstrated that pyrethroids exposure significantly altered the expression of central iron genes, i.e., pyrethroids elevates ferroportin expression in macrophages and represses hepcidin expression in hepatocytes.

5. CONCLUSION:

Based on the present data, oral administration of DLM at doses of 0.87, 8.7 and 17.4 mg/kg b.wt for 9 weeks to male rats causes toxicity. This toxicity is manifested by significant altering iron homeostasis and inducing inflammation through significant increases in inflammatory and immune markers. So, more attention should be given to sources and environmental impact of DLM, with more efforts to limit exposure to which may be a significant contributory factor to the development of Inflammation.

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