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Adverse Developmental and Behavioral Effects of Imidacloprid in Mice

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Abstract

THE PURPOSE of the study was to assess the toxic effects of the imidaclopri (IMI) in mice, as well as on their pups, by determining the LD_{50} using the Dixon method, measuring motor activity and neurobehavioral, supported by histological sections of the brains of pups. The oral LD_{50} dose in both males and females was 113.15 and 107.2 mg/kg respectively. The treated mice with acute doses of IMI showed signs of poisoning represented by salivation, nasal discharge, lacrimation, dyspnea, itching, lethargy, piloerection, tremor, Straub tail, and convulsion in 20 to 100% of the animals. Ranging between oral treatment of pregnant mothers with the IMI at doses of 11 and 34 mg/kg from the 7^{th} to the 15^{th} day of pregnancy led to defects in behavioral measurements, represented by: significant delayed growth differences in the times of pinna opening, lint growth, eye-opening in the treated groups compare to the control group. Also, there was a significant elongation in time postnatal behavior tests which included surface righting reflex and a cliff avoidance test, moreover, the other behavioral tests including the olfactory discrimination test and swimming performance test showed significant differences in lowering of scores in lowering of the sources between treated and control groups as well as histopathological changes in the pups' brains represented by vacuolization in the cortex of the cerebrum, periaxonal edema, neuronophagia, and glial cell satellitosis around neurons, liquefactive necrosis in the cortex of cerebrum with periaxonal edema, glial cells' satellitosis of neurons, gliosis, and neuronophagia. Its concluded that IMI has toxicological effects represented by developmental and neurobehavioral defects enhanced by histological changes in mice.

Keywords: Mice, imidacloprid, developmental, neurobehavioral**.**

Introduction

Insecticides have been widely used in veterinary and agricultural settings, resulting in a variety of environmental disturbances. Their residues can linger in food for extended periods, leading to cancers, neurological, respiratory, and reproductive problems [1,2] .

One broad-spectrum neonicotinoid insecticide, imidacloprid [Imidacloprid (1-(6-chloro-3-pyridylmethyl)-N-nitro-imidazolidin-2-ylideneamine)-IMI] is a popular and efficient neonicotinoid, prevents acetylcholine from transmitting impulses between nerves by competitively inhibiting the nervous system's nicotinic receptors. This builds up choline in the nerve endings, which causes the nervous system to remain stimulated continuously, eventually paralyzing and killing the insect [2].

Neonicotinoids, a novel family of insecticides with structural similarities to nicotine, were developed in response to the developmental neurotoxicity caused by the formerly commonly used organophosphate pesticides. Given their alleged predilection for insects over vertebrate nicotinic cholinergic receptors, neonicotinoids are thought to have lessened this toxicity as compared to organophosphorus insecticides [3]. Furthermore, there was a correlation with the nicotinic receptors found in mammalian neurons. Because neonicotinoids selectively bind to nicotinic receptors in insects while having less of an impact on nicotinic receptors in vertebrates, they are a well-liked substitute for organophosphorous substances in agriculture [4,5]. It is thus thought that fish, birds, and mammals have lower toxicity profiles for imidacloprid and other neonicotinoids. Although it is not very harmful to animals, exposure has a negative health consequences may occur, including

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gastrointestinal problems and neurotoxic effects[6]. As well as immunotoxic, reproductive, mutagenic, and teratogenic consequences with extended exposure [7,8]. While some research on the neurotoxic potential of IMI in rats has been conducted1 [9,10]. It is imperative to learn more about how age affects the neurobehavioral response to IMI exposure in rats [11]. Given that both adults and children may be regularly exposed to IMI through food, drink, or direct contact with pets, as well as previous findings indicating that the effects of other pesticides vary with age [12]. Based on research on animals, it is regarded as somewhat dangerous and may be absorbed by eating cutaneous application, or inhalation [1,2]. The widespread, careless usage of IMI worldwide, owing to its unchecked use and enduring presence in the environment, IMI has found its way into our food chain. Consequently, the individual who is occupationally exposed faces a considerable hazard [5,8 and 9]. The purpose of this study was to elucidate the detrimental developmental and behavioral consequences of imidacloprid in mouse pups, as studies on the neurotoxicity of IMI have not yielded definitive results. The particular objectives of this work were to investigate the idea that prenatal exposure of mice to non-teratogenic doses of imidacloprid treatments causes mild neurotoxic effects that will show up as abnormal behavior during postnatal development.

Material and Methods

Ethics

According to the ethical code number UM. VET. 2021.074. from the Scientific Council of the Department of Physiology, Biochemistry, and Pharmacology, College of Veterinary Medicine, University of Mosul, Iraq, the use of experimental animals and the trials were

Animals

Eighty-three adult white male and female mice, weighing between 20 and 34 grams, who were between the ages of 60 and 90 days. The remaining 105 pups were kept in an animal housing with a 12/12-hour light-dark cycle, free access to food and water.

Imidacloprid preparation

Imidacloprid (emulsified commercial pesticide, 20% concentration, from ; Al-yammama company, and batch number 19133, Jordan) is diluted, with distilled water; every day before use. 10 ml/kg B. Wt. of the medication was administered orally.

The oral median lethal dosage (LD50) of imidacloprid in adult female mice was determined using an up-and-down technique [13].

Six adult female mice (22-23 grams.bw.) were used in this experiment. The first mouse was dosed with 200 mg of imidacloprid orally, and after 24 hours of dosing, we noticed that the mouse remained alive(O) or died (X) . This dose was chosen based on preliminary experiments to determine the average lethal dose using the ascending and descending method for 3 mice after changing the result died or live and versa and calculating imidacloprid LD_{50} relying on Dixon's equation and diagram [13].

LD_{50} =Xf +Kd, in which Xf: the last dose, K: the tabular value, and d: is the value of the dosage rises or falls.

The oral median lethal dosage (LD50) of imidacloprid in adult male mice was determined using an up-and-down technique.

There were seven adult male mice utilized, whose weights varied from 28-37 grams. The first mouse was dosed with 200 mg of imidaclopride orally, and after 24 hours of dosing, we noticed that the mouse remained alive(O) or died (X) . This dose was chosen based on preliminary experiments to determine the average lethal dose using the ascending and descending method for 3 mice after changing the result died or live and versa and calculating imidacloprid LD_{50} relying on Dixon's equation and diagram [13-15].

Recorded signs of acute poisoning of imidacloprid in both female and male adult mice

The study included a group of twenty male and twenty female mice, weighing between 22 to32 g. The mice were given oral doses, and four hours later, the mice were monitored and the acute toxic symptoms of imidacloprid were noted. These groups included the following:

Imidacloprid's 60% LD_{50} acute poisoning effects:

Twenty mice divided into two groups: 1st group 10 adult female mice orally dosed with imidacloprid at (68 mg/kg), While the 2nd group: 10 adult male mice were administered orally with imidacloprid at (64 mg/kg.).

Imidacloprid's 80% LD_{50} acute poisoning effects:

Another twenty mice divided into two groups: 1st group: 10 adult female mice administered orally with imidacloprid at(90 mg/kg). In the 2nd group: 10 adult male mice were administration orally with imidacloprid at (85 mg/kg).

Effects of imidacloprid on the neurobehavioral tests in mice pups from pretreating pregnant mothers

Fifteen mature female mice (mothers; 24 to 36 g b.w.) are divided to 3 groups: The 1st group served as control, while the second and third groups are

treated with imidacloprid at dose of 11.3 mg/kg (10% of LD_{50}) and 34 mg/kg (30% of LD_{50}) respectively. Before treatment of all groups, vaginal smears were taken to determine estrus, to find out the time required to allow males for mating to get pregnant animals. The treatment of the pregnant mice was treated from day 7 till day 15. After birth, the pups(105) were subjected to many measurements including: the earlobe opening time, lint growth time, eye-opening time. Moreover, the following neurobehavioral tests were included : At the fifth postnatal day, the puppy was placed in dorsal recumbency and timed until it successfully righted itself on all four feet. The puppy was allowed a maximum of two minutes to complete the test. This test assesses the integration of neuromotor reflex and vestibular function [16-20].

Cliff avoidance test: This test is conducted on the 6th post-natal day (PND) by placing the pup close to the edge of a table that is high off the ground while observing and recording the time it takes to move away from the edge by turning backward, two minutes was maximum time given to the puppy to complete this test [21]

Olfactory discrimination of home-nest odor test: this test measures nest-seeking the apparatus consists of a plastic container (35×13×12 cm), with two small bins in the side, each one on one side which held bedding, The container has a bin at one end that held dirty bedding from the test puppies' home cage and a bin at the other end that held clean bedding. a wire mesh covering the plastic container, with an empty space in the middle. The pup (9th PND) was positioned on the centrally marked area above the vacant area, and the maximum amount of time permitted was two minutes. The pup had to cross the prescribed line with its front paws and head in order to enter the side of the home cage bedding [16 -20].

Swimming performance test: 1th PND : This test evaluates how well nerve high centers and neuromuscular responses coordinate in response to stressful situations. It is conducted by dropping a mouse into a glass aquarium with water that is 30 cm high and 29–30 degrees Celsius for five to ten seconds, then watching the mouse and recording the results [21,22].

Histopathology: After completion of the behavioral measurements young mice were anesthetized with ether and their skulls were opened to extract the whole brains of all groups which were processed for histopathological examination [17,24].

Statistical analysis

Using the statistical analysis tool SPSS version 16, the parametric findings were first submitted to a least significant difference test and then a one-way analysis of variance (ANOVA) test version 16.0. The Fisher exact test and Mann Whitney U test were used to statistically assess the non-parametric findings, with a $P<0.05$ threshold of significance.

Results

The oral median lethal dosage (LD_{50}) of imidacloprid in adult female mice was determined using an up-and-down technique

The acute LD_{50} of IMI in adult female mice was 113.15 mg/kg, while in adult male mice was 107.2 mg/kg orally, mice treated with IMI showed signs of toxicity represented by salivation, lacrimation, gasping, tremors, muscle fasciculation, convulsions, straub tail, piloerection, ruffled fur, lethargy and finally death may happen at extremely toxic doses (Table 1).

Record signs of acute poisoning of imidacloprid in both female and male adult mice

Oral administration of IMI in adult female and male mice at doses 68 ,90.5 and 64,85.5 mg/kg led to appearance of acute toxic signs that includes salivation, nasal discharge, lacrimation, dyspnea, itching, lethargy, piloerction, tremor, straub tail and convulsion in percentage ranging between 20 to100% (table 2) . While the doses 90.5 and 85.5 mg/kg causes significant decrease in the onset of symptoms, tremor and convulsion time compared with group treated with dose 68mg /kg, as well as the Death ratio were 30% and 40 % respectively (table2).

Effects of imidacloprid on the neurobehavioral tests in mice pups from pretreating pregnant mothers

Oral treatment for pregnant mothers with the IMI at doses of 11 and 34 mg/kg from the 7th to 15th day of pregnancy led to defects in behavioral measurements, represented by: significant delayed growth differences in the times of pinna opening, lint growth, eye-opening between treated groups compare with control group. Also, there was significant elongation in time postnatal behavior tests which included surface righting reflex and a cliff avoidance test, the other behavioral tests including the olfactory discrimination test and swimming performance test showed significant differences in lowering of scores between treated groups compared with the control group table 3.

Histopathological finding

Oral treatment for pregnant mothers with the IMI at doses of 11 mg/kg (10%) from the 7th to the 15th day of pregnancy led to the appearance of histopathological changes in the pups brain represented by vacuolization in the cortex of the cerebrumperiaxonal edema, neuronophagia, and glial

cell satellitosis around neurons (Fig. 2).while the dose of 34 mg/kg (30%) causes liquefactive necrosis in the cortex of cerebrum with periaxonal edema, satellitia's by glial cells around neurons, neuronophagia, and gliosis are (Fig. 3).

Discussion

Neonicotinoids, such as IMI, are well-known for their remarkable efficacy against a variety of pests as well as their very low toxicity to mammals. However, because they agitate insects by changing their nicotinic acetylcholine receptors (nAChRs), mammals may also experience disruptions to the old receptors [25].

In the present study the acute oral LD_{50} of IMI in female and male mice are (113and 107) mg/kg respectively while in the previous study, the LD50 was 130 in males and 170 mg/kg in females [26] , the difference in mean lethal dose values is due to differences in the sex, strains, and species-specific detoxification processes [27] .

The symptoms of cholinergic poisoning seen in our mice correspond to those studies elsewhere in mice that were severely poisoned with IMI [28], IMI works to prevent acetylcholine from transmitting impulses between nerves by competitively inhibiting the nicotinic receptors of the nervous system, leading to the accumulation of choline in the nerve endings, resulting in continuous stimulation of the insect's nervous system, followed by paralysis and death of the insect[28].As well as its association with the nicotinic receptors of neurons in mammals [28]. According to Tomizawa and Casida (2005) the agonist nature of IMI at nicotinic acetylcholine receptors (nAChR) causes neuromuscular paralysis, which is correlated with tremors, convulsions and high respiration rates. Additionally, the rapid onset of toxic symptoms (within 8–14 min) and rapid absorption (92–95% within 1 hour) of IMI are correlated [29], because mammals have resistant nicotinic receptor subtypes compared to insects and the blood-brain barrier protects the central nervous system, animal studies show comparatively low toxicity to mammals [29].

Untargeted animal species, many dietary contaminants, and environmental pollutants can cause oxidative stress and inflammatory responses in the animal brain, which can result in neurobehavioral problems [30-34]. The pups of moms receiving IMI treatment showed comparable behavioral changes. These abnormalities in neurobehavior may indicate nervous system malfunction at different anatomical locations. The brain tissues of the IMI-treated groups showed a variety of pathological changes in the current study. The malfunction at various anatomical locations in the CNS, PNS, and muscle may be the cause of these neurobehavioral deficiencies. Increased AChE activity in the brainstem, cortex, and midbrain was linked to these alterations. While [3H] AFDX 384, a ligand for M2 muscarinic acetylcholine receptors, showed a considerable increase in the cortex, ligand binding densities for [3H] cytosine for α4β2 type nicotinic acetylcholine receptors did not alter appreciably [30,32]. Our work showed that exposure to the IMI decreased neuromotor activity and impaired cognitive effects, along with histopathological changes in the brain, which included perivascular edema and neuronophagia, periaxonal edema, satellitosis by glial cells around neurons and neuronophagia, our results are consistent with other studies [35,36]. The pesticide metabolites such as desnitro metabolite and nitromethylene analog are more toxic in mammals than in insects [37]. Yardimci et al. also noted that increased lipid peroxidation, decreased GSH content, and decreased protein content in the kidneys of male rats exposed to IMI may be linked to increased total cholinesterase activity. The neuronal degeneration seen during the brain histological investigation may be explained by the oxidative damage that ensues [38].

Conclusion

The combined findings of the current research point to the possibility that exposure of pregnant mothers to IMI may cause neurobehaviorally toxic, as seen by decreased exploratory behavior, impaired locomotor activity, and elevated depressive symptoms as well as brain histopathological alteration in pups.

Author's contribution

With the exception of the histopathological reading, which was finished by a pathology specialist, the author did all of the work.

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TABLE 1. Imidacloprid LD_{50} in male and female mice

	Male	Female
Imidacloprid LD_{50}	107.2mg/kg orally	113.15mg/kg orally
Doses range	200-100mg/kg	200-100mg/kg
First dose	200mg/kg	200mg/kg
Last dose	100mg/kg	150mg/kg
Up and down dose mg/kg	50mg/kg	50mg/kg
No. of mice	7(xxxooxo)	6(xxoxoxo)
Onset of toxic signs	8-12 minutes	10-12 minutes

O: mouse still a live , X: mouse dead.

TABLE 2. Acute toxicity signs of imidacloprid in adult female and male mice

Symptoms of toxicity	Females		Males	
	68mg/kg	90.5mg/kg	64mg/kg	85.5mglkg
Salivation and nasal discharge	100%	100%	100%	100%
Lacrimation	100%	100%	100%	100%
Dyspnea	100%	100%	100%	100%
Itching	30%	50%	40%	70%*
Lethargy	70%	100%*	80%	100%*
Piloerection	80%	100%	100%	100%
Tremor	80%	100%	100%	100%
Straub tail	20%	40%	30%	40%
Convulsions	30%	60%*	40%	80%*
Onset of symptoms time	14.3±1.07[ac] minutes	10.2±0.64*[b] minutes	12.8±0.69[ac] minutes	8.7±0.42*[b] minutes
Onset of tremors	36.8±0.74[abc] minutes	24.8±0.84*[c] minutes	28.4±0.97*[c] minutes	19.2±0.91*[ab] minutes
Onset of convulsions	58.2±1.31[abc] minutes	44.8±1.01*[c] minutes	47.2±0.81*[c] minutes	39.6±1.05*[ab] minutes
Dead after 24 hours%	10%	30%	20%	40%*

Values are mean ± SE for 10 mice / group.
* The value differed considerably ($p<0.05$) from the group receiving (68 mg/kg) imidacloprid treatment.
[a] The value differed considerably ($p<0.05$) from the group receiving(90.5 mg/kg) imidacloprid treatment
[b] The value differed considerably ($p<0.05$) from the group receiving (64 mg/kg) imidacloprid treatment.
[c] The value differed considerably ($p<0.05$) from the group receiving (85.5 mg/kg) imidacloprid treatment.

TABLE 3. Neurobehavioral effects of imidacloprid on mice pups from pretreat pregnant mothers

Measurements & neurobehavioral tests	Control	11.3mg/kg	34mg/kg
Pinna opening time(day)	2.23±0.07	2.63±0.13*	3.26±0.18*[a]
Lint growth time (day)	3.86±0.13	4.09±0.17	4.65±0.23*[a]
Eye opening time (day)	15.23±0.07	15.62±0.13*	16.26±0.19*[a]
Surface righting reflex (second)	2.53±0.05	9.93±0.22*	20.27±0.29*[a]
Cliff avoidance test (second)	3.37±0.13	10.79±0.19*	19.77±0.31*[a]
Olfactory discrimination test	0.97±0.02	0.62±0.07*	0.38±0.04*[a]
Swimming performance test	3.91±0.01	3.25±0.1*	2.60±0.08*[a]

Values are mean ± SE for (35) offspring mice from 5 maternal mice/ group.
* The value differed considerably ($p<0.05$) from the group administered saline .
[a] The value differed considerably ($p<0.05$) from the group administered imidacloprid (11.3 mg/kg).

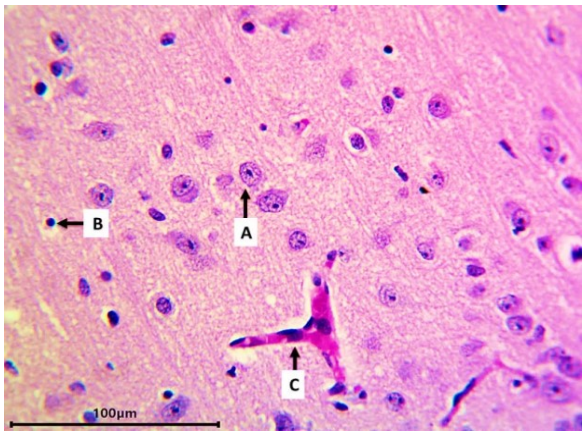

Fig. 1. Image of a control group of mice's brains displaying the cortex of the cerebrum and undamaged neurons (A) glial cells (B) and blood vessels (B). H&E stain, 400X.

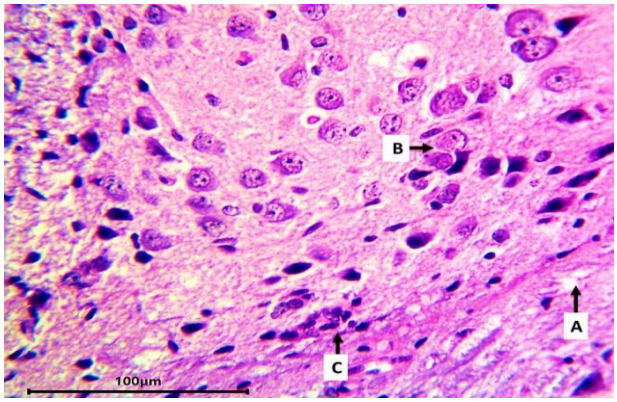

Fig. 2. An image of a 10% group of mice's brains demonstrates the cortex of the cerebrum with vacuolization (A), periaxonal edema (B), glial cell satellitosis around neurons (C), and neuronophagia (D). H&E stain; 100µm scale bar.

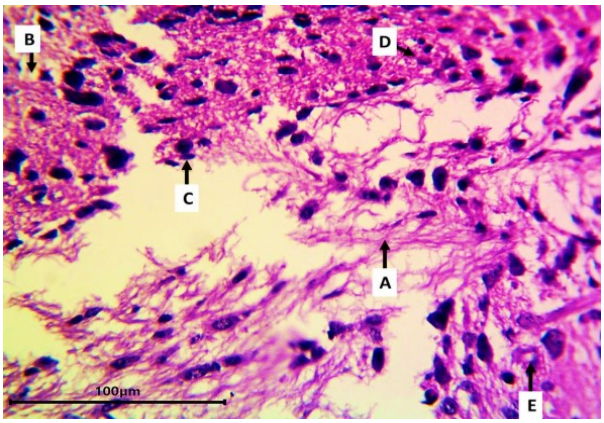

Fig. 3. Image of the 30% group of rats' brains cortex displaying liquefactive necrosis (A), periaxonal edema (B), gliosis (D), neuronophagia (E), and satellitosis by glial cells surrounding neurons (C). H&E stain; 100µm scale bar

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التأثيرات السلوكية والتطورية السلبية للإيميداكلوبريد في الفئران

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الخلاصة

كان الغرض من الدراسة هو تقييم التأثيرات السامة للإيميداكلوبريد (IMI) في الفئران، وصغارها، من خلال تحديد LD50 باستخدام طريقة ديكسون، وقياس النشاط الحركي والسلوك العصبي، مدعومًا بالفحص النسيجي لأدمغة الجراء. وكانت الجرعة المميتة 50 عن طريق الفم في كل من الذكور والإناث 113.15 و107.2 ملغم/كغم على التوالي. أظهرت الفئران المعالجة بجرعات حادة من IMI علامات التسمم المتمثلة في إفراز اللعاب، وإفرازات الأنف، والدموع، وضيق التنفس، والحكة، والخمول، وانتصاب الشعر، والرعشة، وانتصاب الذيل ، والتشنج في 20 إلى 100٪ من الحيوانات. تراوحت المعالجة الفموية للأمهات الحوامل بالـ IMI بجرعات 11 و 34 ملغم/كغم من اليوم السابع إلى اليوم الخامس عشر من الحمل، مما أدى إلى حدوث عيوب في القياسات السلوكية، تمثلت في: اختلافات كبيرة في تأخر النمو في أوقات فتح الصيوان، الوبر. النمو وفتح العين في المجموعات المعالجة مقارنة بمجموعة السيطرة. كما كان هناك استطالة كبيرة في اختبارات السلوك بعد الولادة والتي شملت منعكس تصحيح السطح واختبار تجنب الجرف، علاوة على ذلك، أظهرت الاختبارات السلوكية الأخرى بما في ذلك اختبار التمييز الشمي واختبار أداء السباحة فروقات معنوية في انخفاض الدرجات في خفض المصادر. بين المجموعات المعالجة والسيطرة وكذلك التغيرات النسيجية المرضية في أدمغة الجراء المتمثلة في التفريغ في قشرة المخ، وذمة حول المحور، بلع عصبي، و أقمار الخلايا الدبقية حول الخلايا العصبية، نخر تميع في قشرة المخ مع وذمة حول محور المحور، الخلايا الدبقية ' أقمار الخلايا العصبية، الدباق، و neuronophagia. وتلخصت الدراسة إلى أن IMI له تأثيرات سمية تتمثل في العيوب النمائية والسلوكية العصبية المعززة بالتغيرات النسيجية في الفئران.

الكلمات المفتاحية: الفئران، إيميداكلوبريد، النمو، السلوك العصبي.