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ENZYME ACTIVITY AND TIME-COURSE QUANTITATIVE DISTRIBUTION OF AN ORAL DOSE OF IMIDACLOPRID IN MALE RAT TISSUES

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ABSTRACT: The purpose of this study was to investigate the time course of changes in enzymes activity during distribution of imidaclopride (IMI) in Male Albino rat (*Rattus norvegicus*) after 1, 3, 6, 12, 24 and 48 hr., treatment with a single oral dose (20 mg/kg body weight). The results showed significant gradual increase in liver and kidney function parameters coincided with accumulation of imidacloprid with varying quantities according to each organ, then gradually decreased to the end of study. The highest activity in liver enzymes, ALT (97.33 U/L), AST (78 U/L) ALP (169.66 IU/L) and LDH (5190.67 U/L) was recorded six hours post treatment, as well as increasing in total protein (8.94 g/dl). Kidney function parameters, *i.e.* urea, creatinine and uric acid levels (75.67, 2.283, 19.15 mg/dl, respectively) were also revealed the highest increase comparing with control. Liver and brain acetylcholinesterase (AChE) activity was reached the lowest level with the inhibition percent 82.9, 81.4%, respectively at the same time agreed with the concentration peak of IMI in blood (8.04 µg/ml) liver (2.42 µg/g) and brain (4.06 µg/g). The trend of maximal concentration of IMI in different organs and body fluids at six hours post dosing was in the following order: urine > blood > lungs > brain > testes > spleen > kidney > liver > muscles.

Key words: Imidacloprid, time-course, residues, enzymes, QuEChERS, male rats.

INTRODUCTION

Neonicotinoids group is a new class of systemic insecticides having the same structure and action of nicotine, therefore acts as agonists at the insect nicotinic acetylcholine receptors (nAChRs) in post synaptic (**Yamamoto *et al.,* 1998; Matsuda *et al.,* 2001**).

Among them, imidacloprid (IMI) is being the first compound introduced into the global market since 1991 (**Moriya *et al.,* 1992**). It is moderately toxic and its acute oral LD_{50} is 450 mg/kg for rats and 150 mg/kg for mice (**Tomlin, 1997**). Due to increasing use of IMI in agriculture to control piercing-sucking insect pests, its residue may occur in foods, fruits and vegetables, and therefore, pose a potential hazard for consumers (**Watanabe et *al.,* 2007**). IMI, according to the Environmental Protection Agency, has the potential to leach into groundwater and runoff due to its high solubility (0.61 g/l) and mobility which contaminate water. IMI has selective toxicity resulted from its high affinity to insect's nicotinic acetylcholine receptors versus mammals (**Tomizawa and Casida, 2005**). The liver is the principal target organ of imidacloprid toxicity, as demonstrated by elevation of serum activities of aspartate aminotransferase (AST), alkaline phosphatase (ALP) and lactate dehydrogenase. Exposure to 1/100 LD_{50} of IMI induces immunotoxicity, oxidative stress, lipid peroxidation and hepatotoxicity in male rats (**Rahman *et al*., 2000; Mohany *et al.,* 2011**). IMI caused significant decrease in acetylcholinesterase activity in brain and plasma after oral dose for 60 days (**Vohra *et al.,* 2014**). IMI has toxicological effect at a dose level of 20

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mg/kg/day after 90 days oral administration, causing damages in morphology of ovary, ovarian hormones, and the activity of antioxidant enzymes in female rats. IMI at 5 and 10 mg/kg/day has not produced any significant changes and induced significant effects on body weight, liver and kidney functions at 15 mg/kg/ day to mice (**Kapoor *et al*., 2011; Arfat *et al*., 2014**). Tissue disposition can provide important information on the time-course of compound transfer from one tissue compartment to another. **Kapoor *et al.* (2014)** used QuEChERS, which stands for quick, easy, cheap, effective, rugged, and safe method for analysis the residues of IMI in different organs (liver, brain, kidney and ovary) and body fluids (blood, urine and faeces). **Taliansky-Chamudis *et al.* (2017)** showed that QuEChERS is a successful technique for analysis of neonicotinoids including IMI in blood of eagle owls. They found a good range of recoveries ensuring the use of these techniques for monitoring studies successfully. Increasing use of imidacloprid and its potential toxicity among human heightened its warrants toward awareness. The objective of the current study is to evaluate the time course effect following single oral dose of IMI in male rat tissues and blood. Thus, we have tried to correlate the tissue concentration of IMI with tissue disposition and biochemical effects.

MATERIALS AND METHODS

Animals

Male albino Wistar rats (*Rattus norvegicus*) weighing 160 ± 10 g were obtained from the Laboratory Animal Housing Unit, Faculty of Veterinary Medicine, Zagazig University, Egypt, and acclimatized for 2 weeks prior to the experiment in plastic cages under laboratory conditions (22±3°C, relative humidity 65 ± 5% and a 12 hr., light/dark cycle). Rats were treated individually in metabolic cages with free access to food and water. All experimental procedures were approved by the Institutional Animal Care and Use Committee, Zagazig University (ZU-IACUC) (Number: ZU-IACUC/2/F/59/2018).

Insecticide

A technical grade sample of Imidacloprid 98% ((E) – 1 - (6 – chloro – 3 – pyridylmethyl) –N – nitroimidazolidin – 2 – ylideneamine) was obtained from Sumitomo Chemicals Co.Ltd.

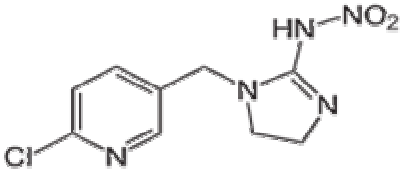

Fig. 1. Chemical structure of imidacloprid

Chemicals

Acetonitrile, HPLC grade (POUCH SA, Gliwice, Poland); glacial acetic acid (El-Nasr Pharmaceutical Chemicals Co., Abu-Zaabal, Cairo, Egypt); primary secondary amine (PSA), C18 and anhydrous magnesium sulfate ($MgSO_4$) for QuEChERS kits purchased from Agilent Technologies Co. (USA). Aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP), lactate dehydrogenase (LDH), total protein, Blood urea nitrogen (BUN), uric acid, creatinine and Acetylcholinesterase (AChE) kits were obtained from Bio-diagnostic Chemical Company, Cairo, Egypt.

Animals Treatment

A single oral dose from Imidacloprid (IMI) (20 mg/kg b. wt.) 1/22 of LD_{50} was dissolved in corn oil as vehicle and administered to rats. Sixty animals were randomly divided into two groups. Group I (30 rats) served as vehicle control and was given corn oil (0.4 ml/rat) through gavage. Group II (30 rats) was orally administered IMI (20 mg/kg b. wt.) suspended in corn oil in single dose with equal volume of oil per rat. Five animals from control and five animals from treated groups were sacrificed at 1, 3, 6, 12, 24 and 48 hr.

Blood and Tissue Samples

At each time point, two blood samples were immediately collected from each rat. The first sample collected into heparinized tubes for IMI residues analysis. The second sample was collected in a non-heparinized tube and centrifuged for 10 min at 3000 rpm to separate the serum, which was then stored at -20°C for further biochemical analysis. Liver, kidney, testes, lungs, muscles spleen and brain organs were removed after dissection. However urine

samples were collected at 6 hr., 12 hr., 24 hr. and 48 hr. All samples were stored at -20°C until analysis.

Biochemical Analyses

Liver and kidney biomarkers

Liver and kidney function biomarkers; serum Aspartate aminotransferase (AST), alanine aminotransferase (ALT) activities and alkaline phosphatase (ALP) activity were determined colorimetrically, using UV-VIS spectrophotometer (Perkin-Elmer 550 SE, Germany) at 546, 546 and 510 nm, respectively according to **Henry (1964)**. Lactate dehydrogenase (LDH) activity as an indicator of necrotic cell death was determined using diagnostic kit according to **Vassault (1986)**. Total protein was measured colorimetrically according to the method of **Vassault (1986)** using the kit obtained from Bio-diagnostics. Creatinine, uric acid and blood urea nitrogen (BUN) were measured colorimetrically according to the method of **Henry (1974), Trinder (1969) and Chaney and Marbach (1962)**, respectively.

Acetylcholinesterase (AChE) activity

Acetylcholinesterase (AChE) activity was measured in liver and brain with a colorimetric method according to the method of **Ellman *et al.* (1961)**.

Residue Analyses

Imidacloprid residues in blood, liver, kidney, spleen, brain, lung, muscles and urine were determined. Three samples from each organ were extracted and cleaned up using QuEChERS modified method according to **Lehotay (2007) and Kapoor *et al.* (2014)**. The residues of IMI were determined using HPLC system (Agilent, USA) model 1100 series with the following conditions: a binary pump and auto sampler, UV (Ultra violet detector), BDS C_{18} Equisil column (4.6 mm (id)×150mm length) and the mobile phase was distilled water and acetonitrile (30:70, *V/V*). The flow rate was maintained at 1.0 ml/min and the injection volume was 10 µl. IMI was detected at 270 nm at retention time 2.9 min. Results were corrected using their respective recovery rates.

Statistical Analysis

Data of biochemical and residues analyses were presented as the mean ± standard deviation. Co-Stat Windows software package was used for statistical analyses. Duncan and Tukey-Test at $P < 0.05$ were assessed as statistical significance (**Anonymous, 1986**).

RESULTS AND DISCUSSION

Tissue Distribution of Imidacloprid in Rats

Results in Table 1 show the detected residue amounts of IMI in different organs and body fluids of male Wister albino rats after 1, 3, 6, 12, 24 and 48 hr., of oral administration. There was a rapid distribution of the insecticide IMI in rat tissues one hour after single oral administration (20 mg/kg b. wt.). Residues in the tested tissues at 48 hr., after dosing recorded minimal concentrations. After 6 hours, the general trend of maximal concentration of IMI residues was in the following order: urine > blood > lung > brain > testes > spleen > kidney > liver > muscles. The level of IMI was 25.62 and 8.04 µg/ml in urine and blood and 7.52, 4.06, 3.99, 3.79, 3.14, 2.42 and 2.05 µg/g in lung, brain, testes, spleen, kidney, liver, muscles, respectively. As shown in Table 1 when time elapsed, the concentrations of IMI in the tested tissues were increased to reach the maximum amounts after 6 hours with the exception of muscles and urine (after 12 hr), which indicates the absorption of IMI in rats reached to saturation post dosing, then decreased gradually to reach to the minimum detected amounts at the end of the experimental period (48 hr.) in blood, urine, lung, brain, spleen, kidney, liver, testes and muscles recording 0.19, 1.87, 0.16, 0.09, 0.09, 0.11, 0.21, 0.12 and 2.13 µg/ml or g, respectively.

Results also revealed that the concentration in the muscles (0.07 µg/g) was lower than the other organs, *i.e.* blood, lung, brain, spleen, kidney, liver and testes after one hour post dosing (2.81, 3.24, 1.89, 2.08, 1.51, 0.59 and 0.29 µg/g or ml, respectively). The pattern of distribution of IMI in different organs and body fluids was varied, however, the occurrence of peak levels of IMI at the 6 hr., time

Table 1. Distribution of imidacloprid in different organs and body fluids of male Wister albino rats following single oral administration (20mg/kg body weight)

Sample	Detected amount (µg/g or µg/ml) of imidacloprid at*					
	1 hr.	3 hr.	6 hr.	12 hr.	24 hr.	48 hr.
Blood	2.81±0.16	4.06±0.04	8.04±0.18	3.76±0.17	0.35±0.001	0.19±0.002
Brain	1.89±0.18	2.13±1.09	4.06±1.04	1.72±0.30	0.19±0.01	0.09±0.01
Liver	0.59±0.06	0.85±0.03	2.42±0.04	0.78±0.01	0.39±0.05	0.21±0.02
Kidney	1.51±0.01	1.80±0.14	3.14±0.06	1.59±0.02	0.13±0.002	0.11±0.02
Spleen	2.08±0.05	2.670.02	3.79±0.03	1.05±0.01	0.29±0.03	0.09±0.01
Testes	0.29±0.03	1.21±0.22	3.99±0.13	1.86±0.19	0.19±0.01	0.12±0.002
Muscles	0.07±0.01	0.51±0.61	2.05±0.32	5.55±0.41	2.26±0.06	2.13±0.11
Lung	3.24±0.07	5.95±0.01	7.52±0.03	3.13±0.08	0.32±0.01	0.16±0.03
Urine	NA**	NA	25.62±0.18	31.96±2.86	13.55±0.29	1.87±0.001

* Detected amounts of imidacloprid in blood and urine (µg/ml) while in the rest samples (µg/g).
**samples from urine were not collected after 1 and 3 hr., of treatment.

point in all tissues suggests that IMI was rapidly absorbed, distributed, metabolized and excreted after oral administration as indicated by its presence in blood, urine and organs. Protein binding in the blood can be assumed to play a significant role with IMI in illustrating its fate in the body for periods of time. These results are agree with those obtained by **Brunet *et al.* (2004)** who reported that IMI is highly absorbed in human intestinal cell suggesting its potential effects. No difference was found between female and male rats. Concentration peaks of IMI were attained by 6 hr in all tissues, with the exception of the muscles and urine, 12 hr. Meanwhile, **Kapoor *et al.* (2014)** reported that the concentration of IMI was maximum attained at 12 hr., post dosing in organs (liver, brain, kidney and ovary) and body fluids (blood, faeces and urine) after the same dose (20 mg/kg b. wt.) in female rats.

Enzymes Activity

With respect to enzymes activity, the levels generally agreed quite well with the presence in the target tissues, *i.e.,* the greater the amounts of compound presents at the time point, the greater the levels of enzymes observed. It is clear that the presence of IMI, specifically at peak concentration, in the selected tissues appears to be a good indicator of enzymes reduction. A shift in the amount and rate of oral absorption may result in the observed alteration in the time course of both parent compound and its metabolites resulting an increase and delay in achieving to the maximum concentration **(Timchalk *et al.*, 2006)**. Changes in serum levels of AST, ALT, ALP and LDH enzymes and the levels of blood urea nitrogen (BUN), creatinine, uric acid and total protein showed a dose-related time course of IMI exposed groups. These results are in agreement with those obtained by **Abu Zeid *et al.* (2019)**.

Liver function

The effect of IMI on serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) activities are shown in Table 2. The highest significant increase in enzymes activity was recorded 6 hr., after dosing, then less increase were observed up to the end time point, 48 hr., of the study.

Comparing with control, ALT, AST and ALP were significantly increased at all the time periods of the experiment after dosing. As for LDH, the enzyme activity was increased significantly one hr. post dosing, whereas there were significant increases up to the end point; *i.e.* 48 hr. The increases in enzyme activities were not significant at 3 and 48 hr for ALT and LDH, as well as at 6 and 12 hr., with LDH only.

Table 2. The effect of imidacloprid on liver enzymes in male rats after single oral administration (20 mg/kg body weight)

Time (hr.)	ALT (U/L)	AST (U/L)	ALP (IU/L)	LDH (U/ L)
Control	15.66 ± 1.25 [f]	24.33 ± 2.05 [f]	68.66 ± 2.49 [g]	2824.00 ± 10.98 [d]
1	25.33 ± 2.62 [e]	41.00 ± 2.16 [d]	82.66 ± 2.62 [f]	3114.17 ± 131.61 [d]
3	39.66 ± 3.39 [d]	51.66 ± 2.87 [c]	98.66 ± 6.01 [e]	3813.66 ± 118.38 [c]
6	97.33 ± 2.29 [a]	78.00 ±2.16 [a]	169.66 ± 3.39 [a]	5190.67 ± 77.14 [a]
12	82.00 ± 3.74 [b]	64.00 ±3.27 [b]	146.00 ± 5.89 [b]	4862.67 ± 45.09 [a]
24	64.00 ± 2.45 [c]	47.33 ± 2.62 [c]	124.66 ± 4.11 [c]	4357.66 ± 477.09 [b]
48	41.67 ± 2.87 [d]	33.00 ± 3.56 [e]	113.00 ± 4.55 [d]	3583.33 ± 209.49 [c]

Values are mean ± S.D. (n=5/group). Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline phosphatase (ALP), Lactate dehydrogenase (LDH).

Increasing in enzyme activities at 6 hr may be due to the high accumulation of IMI at this time in the liver as it is the principal target organ for any foreign compound entering the body. These results are in agreement with those obtained by **Bhardwaj *et al.* (2010), Balani *et al*. (2011), Mohany *et al.* (2011), Toor *et al.* (2013), Arfat *et al.* (2014), Kapoor *et al.* (2014) and Abu- Zeid *et al.* (2019)**.

Kidney functions

The effects of IMI on serum levels of blood urea nitrogen (BUN), creatinine, uric acid and total protein are shown in Table 3. There was significant increase in level of urea, uric acid and total protein, and insignificant increase in the level of creatinine after one hour post dosing single oral dose compared to control group. The levels continued to show significant increase until reached to the time of peak effect at 6 hr., after dosing, while their levels significantly ($p<0.05$) decreased after 12 hr., up to the end of the experimental period (48 hr.). The results suggest that the higher accumulation of IMI at 6 hr., cause significant increase in the levels of (BUN), creatinine, uric acid and total protein but at the end of study these levels decreased and reached to the normal level that does not cause any toxicity. In this respect, **Bhardwaj *et al.* (2010)** studied the IMI nephrotoxicity and found tubular changes in the kidney in rats when exposed to higher dose.

Arfat *et al.* (2014) also found that higher doses of IMI increased tubular changes and show its nephrotoxicity in mice. However, the kidneys, the major detoxification organ for many xenobiotics, are frequently susceptible to the nephrotoxic effects. We also found that higher accumulation of imidacloprid after 6 hr., of administration caused significant changes in the kidney function.

Acetylcholinesterase activity

Liver and brain acetylcholinesterase activity are shown in Table 4. There was a significant reduction in the level of acetylcholinesterase activity after one hour post dosing single oral dose compared to control group. The reduction level continued to show significant increase until reached the time of minimal level at 6 hr., post dosing, then the rate of reduction of enzyme activity was lesser in the followed time intervals up to the end point time; *i.e.* 48 hr., of the study.

The extent of AChE inhibition was almost comparable in liver and brain at 3-24 hr., post dosing. The inhibition of AChE ranged from 21% to 82% in liver and 27–81% in brain as compared to the control. The reason of AChE inhibition is unknown because IMI is not AChE inhibitor, since plasma AChE is synthesized in the liver, the decrease in plasma AChE activity may be related to observed changes in liver function (**California EPA, 2006**).

Table 3. Effect of imidacloprid on the level of urea, creatinine, uric acid and total protein in the serum of males Wister albino rats

Time (hr.)	Urea (mg/dl)	Creatinine (mg/dl)	Uric acid (mg/dl)	Total protein (g/dl)
Control	28.00 ± 2.16 ^{e}	0.75 ± 0.03 ^{f}	5.68 ± 0.11 ^{g}	7.25 ± 0.10 ^{e}
1	38.00 ± 0.82 ^{d}	0.92 ± 0.04 ^{ef}	7.20 ± 0.03 ^{f}	7.68 ±0.08 ^{d}
3	51.33 ± 2.49 ^{c}	1.05 ± 0.05 ^{e}	10.13 ± 0.07 ^{d}	8.04 ± 0.06 ^{c}
6	75.67 ± 2.62 ^{a}	2.28± 0.13 ^{a}	19.15 ± 0.26 ^{a}	8.94 ± 0.23 ^{a}
12	62.33 ± 2.05 ^{b}	1.98 ± 0.02 ^{b}	13.15 ± 0.12 ^{b}	8.53 ± 0.16 ^{b}
24	51.66 ± 1.25 ^{c}	1.49 ± 0.15 ^{c}	11.41 ± 0.18 ^{c}	8.16 ± 0.07 ^{c}
48	40.67 ± 1.69 ^{d}	1.31 ± 0.08 ^{d}	8.85 ± 0.12 ^{e}	7.93 ± 0.13 ^{cd}

Values are mean ± SD (n=5/group).

Table 4. Acetylcholinesterase activity in liver and brain of male rats after single oral administration of imidacloprid (20 mg/kg b. wt.)

Time (hr.)	Liver		Brain	
	(ng/ml)	Decrease (%)	(ng/ml)	Decrease (%)
Control	5.26 ± 0.08 ^{a}	-	16.54 ± 0.45 ^{a}	-
1	4.11 ± 0.06 ^{b}	21.8631	11.995 ± 0.09 ^{b}	27.4788
3	3.01 ± 0.06 ^{c}	42.8707	9.67 ± 0.13 ^{c}	41.5357
6	0.90 ± 0.04 ^{e}	82.8897	3.07 ± 0.51 ^{e}	81.4389
12	1.27 ± 0.03 ^{e}	75.8555	3.705 ± 0.26 ^{e}	77.5998
24	1.995 ± 0.06 ^{d}	62.0722	6.215 ± 0.12 ^{d}	62.4244
48	2.87 ± 0.03 ^{c}	45.4373	9.03 ± 0.37 c	45.4051

Values represent the mean ± SD. (n=5/group).

Earlier studies showed that oral administrations of IMI to albino rats were significantly altered AChE levels in different regions in brain, plasma, serum, liver and blood (**Bhardwaj *et al*, 2010; Kishandar *et al*, 2010; Boily *et al*., 2013; Kapoor *et al*, 2014; Vohra *et al*, 2014**). **Vohra and Khera (2015)** reported that the brain and plasma AChE activity in rats was significantly reduced at 1/22 LD_{50} of imidacloprid.

Marzouk (2016) found that after 24 hr., rats treated orally with imidacloprid (1/10 LD_{50}), no changes were detected in brain AChE level, whereas a slight decrease was recorded in serum AChE.

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النشاط الإنزيمي والمسار الزمني للتوزيع الكمي لجرعة فمية من الايميداكلوبريد في أنسجة ذكور الجرذان

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يهدف البحث لدراسة التغيرات في نشاط الإنزيمات والمسار الزمني لتوزيع الإيميداكلوبريد في أنسجة ذكورالجرذان البيضاء بعد ١ ، ٣ ، ٦ ، ١٢ ، ٢٤ و ٤٨ ساعة من المعاملة بجرعة فمية واحدة (٢٠ ملجم/كجم من وزن الجسم)، وقد أظهرت النتائج زيادة تدريجية في وظائف الكبد والكلى تزامنت مع تراكم الإيميداكلوبريد بكميات متفاوتة حسب كل عضو ثم انخفضت تدريجياً إلى نهاية الفترة الزمنية للدراسة، وتم تسجيل أعلى نشاط في إنزيمات الانين امينو ترانسفيراز (٩٧,٣٣ وحدة/لتر) والكالين فوسفاتيز (٧٨ وحدة/لتر) واسبرتات امينو ترانسفيراز (١٦٩,٦٦ وحدة دولية/لتر) ولاكتات ديهيدروجينيز (٥١٩٠,٦٧ وحدة/لتر) في المعاملة بعد ست ساعات، وكذلك زيادة في البروتين الكلي (٨,٩٤ جم/ديسيلتر)، كما تم توضيح مستويات حمض اليوريا والكرياتينين وحمض اليوريك (٧٥,٦٧ ، ٢,٢٨٣ و١٩,١٥ ملجم/ديسيلتر على التوالي) وهي أعلى زيادة عند نفس الزمن مقارنة بالكنترول، انخفض نشاط الاستيل كولين استريز في الكبد والمخ بعد ست ساعات من المعاملة بنسبة ٨٢,٩ و٨١,٤% على التوالي متزامنا مع ذروة تركيز الايميدكلوبريد في الدم (٨,٠٤ ميكروجرام/ملي) الكبد (٢,٤٢ ميكروجرام/جم) والمخ (٤,٠٦ ميكروجرام/جم)، وكان ترتيب أقصى تركيز للايميداكلوبريد في مختلف أعضاء الجسم وسوائله بعد ست ساعات من المعاملة كالتالي: البول > الدم > الرئتين > المخ > الخصيتين > الطحال > الكلى > الكبد > العضلات.

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