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POSTNATAL TOXICITY OF ABAMECTIN IN RABBITS

BY

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ABSTRACT

To evaluate maternal and fetal toxicity induced by abamectin pesticide (Vertimec) in female rabbits during lactation period, twelve pregnant New Zealand white rabbits were divided into two groups (6 for each). The first group was used as control and received orally distilled water. The second group was orally administered 2mg/kg B.wt of abamectin from first day of parturition till 30th day of lactation. Body weight of fetuses was recorded every week for one month. The two groups (dams and their fetuses) were sacrificed at 30th day of lactation. Blood samples were collected from dams and their fetuses for hematological examination. Sera samples were separated for biochemical analysis. Liver, kidney, spleen and brain from both dams and their fetuses were preserved in neutral buffered formalin for histopathological examination. The results revealed a significant decrease in fetal body weight during lactation period compared to control group. Hematological analysis of dams revealed that total count of white blood corpuscles (WBCs) and the values of PCV were non-significantly altered. Serum activities of AST and ALP enzymes were significantly increased, but ALT activity was not altered. The activity of GST and SOD enzymes were significantly decreased, but nitric oxide (NO) levels were increased. For fetuses, there was a significant increase in total count of WBCs, PCV values and Hb concentrations. Sera samples of fetuses revealed a significant increase in ALT, AST ALP and SOD enzymes activities. GST enzyme activity was decreased. Nitric oxide (NO) levels were increased. Histopathological examination revealed pathological changes in liver, kidney, spleen and brain tissues in both dams and fetuses. This study indicated that abamectin has deleterious effects on both mother and fetuses during lactation period.

INTRODUCTION

The avermectins (AVMs) are compounds derived from the fermentation of the soil bacterium *Streptomyces avermitilis*. This group includes abamectin, ivermectin and doramectin, which are highly effective against a broad spectrum of common pests in agriculture, making avermectins one of the most widely used classes of parasiticides **(Campbell, 1989; Kovecses and Marcogliese, 2005).** Abamectin is a mixture that contains about 80% avermectin B1a and 20% avermectin B1b, which have similar biological and toxicological properties **(Lankas and Gordon, 1989; Fisher and Mrozik, 1992).** AVMs act mainly on the nervous system of organisms and although the antiparasitic activity of AVMs was first described in 1979, its action mechanism has not been fully elucidated. However, it is usually related to GABAergic receptors (γ- aminobutyric acid) in invertebrates as well as vertebrates, and glutamate-gated chloride channels in invertebrates. Most authors mention that the AVMs can act not only as GABA agonists, but also can stimulate the release of GABA in the presynaptic inhibitory terminals. In both cases, they increase the permeability of chloride ions, hyperpolarizing the nerve and muscle cells, ultimately interfering with neuromuscular transmission, leading to death **(Cully et al., 1994**). Abamectin poisoning can impair the function of hepatocytes.

Research conducted by **Hsu et al., (2001)** showed elevated activity of the enzyme aspartate aminotransferase (AST) in the blood serum of rats after exposure to abamectin by gavage at doses between 1 and 20 mg/kg body weight. The maximum activity was obtained with a dose of 20 mg/kg of body weight 1h after ingestion. **Eissa and Zidan (2010)** using a commercial product, and observed signs of liver toxicity, with increased activity of the enzyme AST activity in rats treated with doses equivalent to 1/10 or 1/100 of the LD50 (18 mg/kg) in the diet of animals over 30 consecutive days. In addition, **El-Shenawy (2010)** undertook a comparative study of the in vitro toxic action of some insecticides, including abamectin at concentrations of 10 and 100 μM, on isolated rat hepatocytes. There was a significant increase in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activity when hepatocytes were incubated for 30 min with both concentration. This activity persisted after 120 min.

The effects of ivermectin on preweaning rat pup mortality, growth, and behavior were examined in a study that orally administered 1, 2, or 4 mg/kg/day from gestation days 6 to 20 and lactation days 2 to 20. Increased pup mortality, delayed growth, and effects on various

reflex and behavioral tests were observed in the 2 and 4 mg/kg/day groups, whereas in the 1 mg/kg/day group only cliff avoidance and locomotion were affected **(Poul, 1988).**

The aim of this study was to evaluate the maternal and fetal toxic effects of abamectin when administered during lactation period.

MATERIAL AND METHODS

Tested insecticide:

The tested insecticide was abamectin, (Vertimec^{R}) 1.8%EC, Syngenta Company; used as an acaricide. A mixture containing a minimum of 80% avermectin B_{1a} (5-O-demethylavermectin A_{1a}) and a maximum of 20% avermectin B_{1b} (5-O-demethyl-25-de-(1-methylpropyl)-25-(1-methylethyl) avermectin A_{1a}.

Experimental animals and Design:

Twelve mature female New Zealand white rabbits, weighing 3 to 3.5 kilogram and aged about 4.5 to 5 months old were obtained from Animal Experimental Unit, Faculty of Agriculture, Mansoura University. The animals were apparently clinically healthy. Animals were housed in separate batteries and kept under controlled condition (23±1^{o}C), 12h light and 12h dark cycle. Rabbits were fed on standard laboratory pelleted diet and water ad. Libitum. They were accommodated for our laboratory condition for 2 weeks before starting the experiment. Dams were caged with male and zero day of pregnancy was detected then the pregnant rabbit were randomly distributed into two groups (6 for each). The first group used as control and received orally distilled water. The second group was orally administered 2mg/kg B.wt of abamectin from first day of parturition till 30th lactational day. Dams and their fetuses were observed twice daily for signs of treatment-related effects and body weight of fetuses was recorded every week for one month. At 30th day of lactation, both dams and their fetuses were sacrificed.

Blood samples

Blood samples from dams and their fetuses were collected immediately after sacrificing in dry clean centrifuge tubes. One portion was taken on EDTA as anticoagulant for haematological examination. The other portion was collected without anticoagulant and left to clot at room temperature for about 20 min. and then centrifuged at 3000 r.p.m for 15 minutes; the serum was drown in dry clean-capped tubes and kept in deep freezer at-20ºC until conducting the biochemical analysis.

Haematological Examination

Total leukocytic count (TLC): Leukocytes were counted (**Feldman et al.,2000**). Hemoglobin concentration (Hb): (**Drabkin,1949).** Packed cell volume (PCV)(**Coles, 1986).**

Biochemical Analysis

Liver function tests: Aspartate and Alanine aminotransferase (AST and ALT) activities of (**Reitman and Frankel 1957).** Alkaline phosphatase (ALP) activity (**Belfield and Goldberg 1971)**. Antioxidant levels: Glutathione-S-transferase (GST) (**Habig and Pabst (1974)** and Superoxide dismutase (SOD) **Nishikimi (1972)**. Nitric oxide (NO) (**Montgomery and Dymock 1961).**

Histopathological study

Specimens from liver, kidney, spleen and brain were preserved in 10% neutral buffered formalin. Sections of 5 micron thickness were prepared and stained by hematoxyline and eosin (H&E) and examined microscopically according to **Bancroft et al., (1990).**

Statistical Analysis

Statistical analysis was carried out **(Snedecor and Cochran, 1984),** the different variables were analyzed using Student's (t) test.

RESULTS

1. Effect of abamectin on rabbit dams

Hematological Parameters :

There was non-significant difference in the values of PCV, Total Leukocytic Count and Hb concentration table (1), fig. (1,2,3)

Biochemical parameters:

There was non-significant difference in the activity of alanine aminotransferase enzyme (ALT). While, there was a highly significant increase in the activities of aspartate aminotransferase enzyme (AST) and alkaline phosphatase enzyme (ALP). In addition, there was a highly significant decrease in the activities of GST enzyme and SOD enzyme. NO levels were highly significantly increased.

Table (1): Effect of abamectin on some hematological and biochemical parameters of rabbit dams during lactation period (Mean ± SE).

Group	ALT U/ml	AST U/ml	ALP IU/L	SOD U/ml	GST U/L	NO Mmol/L	PCV %	Hb g/dl	TLC $10^3/\mu L$
Postnatal Control	13.93 ± 0.12	15.62 ±0.39	8.17 ± 1.85	345.80 ±4.53	3201.8 ±86.63	8.03 ± 0.33	42.20 ± 0.58	9.794 ± 0.23	8.02 ± 0.32
Postnatal 2 mg/kg	13.75 ± 0.21	30.13* ±0.35	49.33* ±1.54	218.3* 4.20±	1804.7* ±52.17	11.18* ±0.23	40.00 ± 1.52	10.728 ± 0.36	7.66 ± 0.46

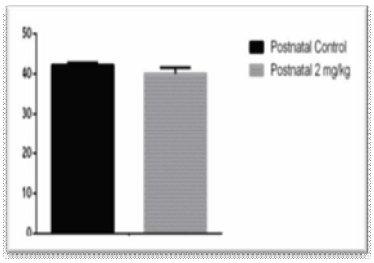

Fig.(1): PCV values

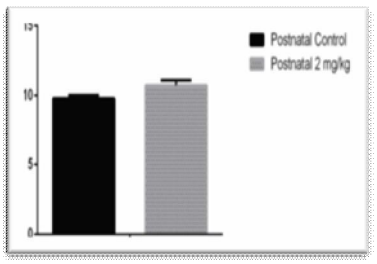

Fig.(2): Hb values

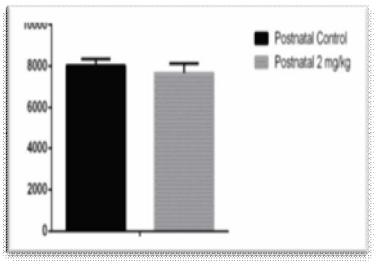

Fig.(3): TLC values

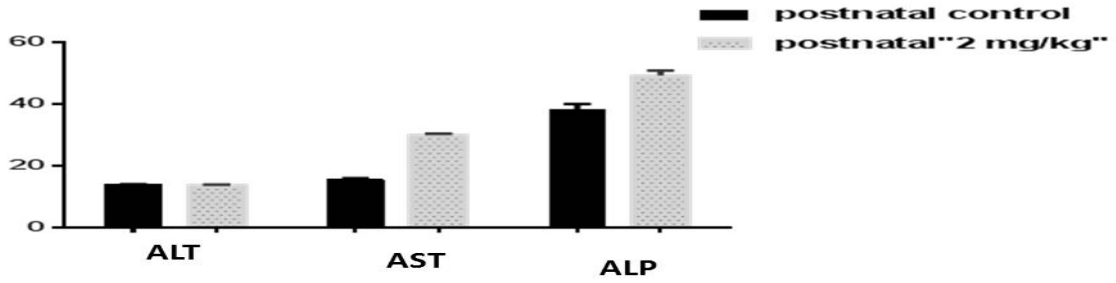

Fig. (4)Transaminases and Alkaline phosphatase activities.

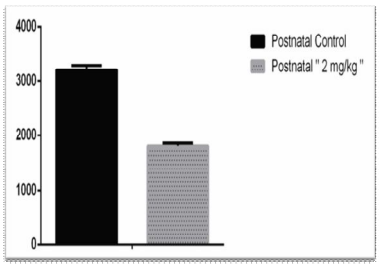

Fig.(5): GST values

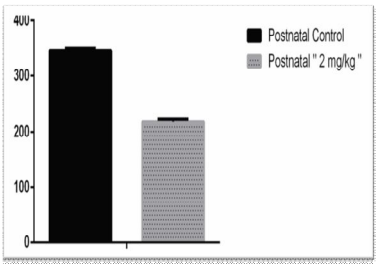

Fig.(6): SOD values

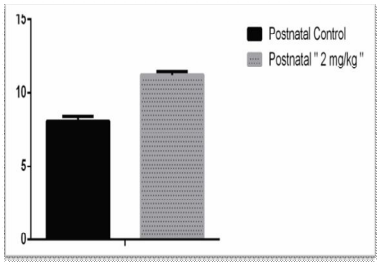

Fig.(7): NO values

2. Effect of abamectin on suckling fetuses

Effect on body weight :

A significant decrease in body weight of foeti during 1st week compared to control. A highly significant decrease in body weight of foeti during 2nd, 3rd and 4th week compared to control.

Table (4) Weight of foeti from dams orally administered abamectin during lactation period (Mean±SE):

period	Control group (gm.)	Group 2mg /kg (gm.)
Initial bodyweight	37.1 ± 1.10	36.9 ± 1.05
1st Week .	73.5 ± 2.98	63.50* ± 1.83
2nd Week .	195.5 ± 5.02	152.0* ± 5.88
3rd Week .	304.5 ± 7.97	230.0* ± 5.92
4th Week .	423.5 ± 10.78	329.0* ± 8.49

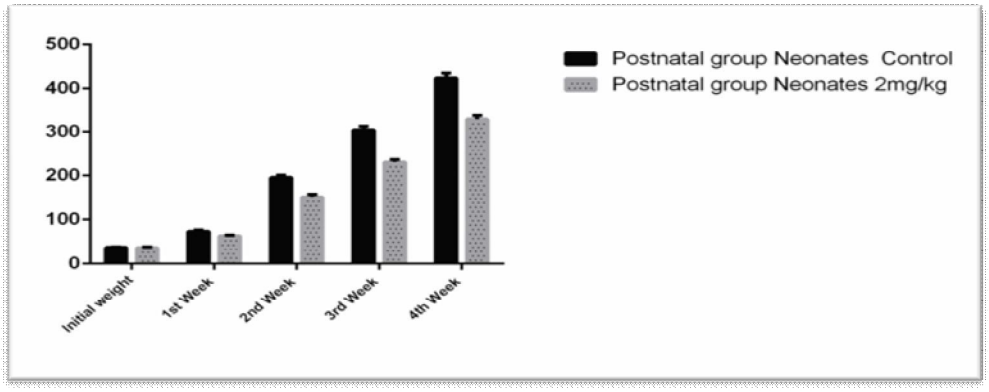

Fig.(8): Body weight of suckling fetuses from dams orally administered abamectin during lactation period.

Haematological parameters:

There were non-significant in the values of PCV and hemoglobin concentration . A highly significant increase in the total leucocytic count.

Biochemical parameters:

There were a significant increase in the activities of ALT, AST and ALP enzymes. While, GST enzyme activity was highly significantly decreased. SOD enzyme activity was significantly increased. Nitrogen oxide (NO) levels were highly significant increased.

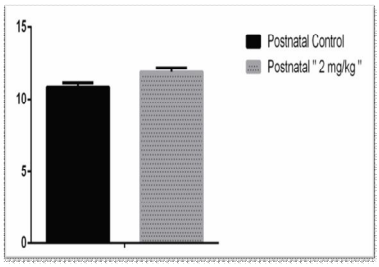

Fig.(9): PCV values

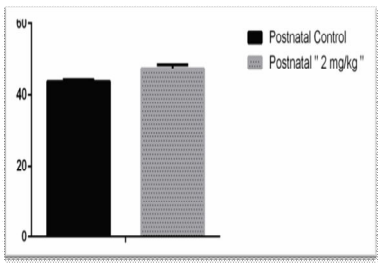

Fig.(10): Hb values

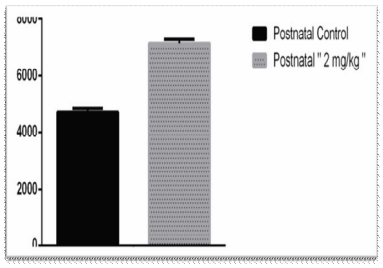

Fig.(11): TLC values

Table(6): Hematological and biochemical parameters of suckling feti from dams treated with abamectin during lactation period (Mean ± SE).

Group	ALT U/ml	AST U/ml	ALP IU/L	GST U/L	SOD U/ml	NO Mmol/L	PCV %	Hb g/dl	TLC $10^3/\mu L$
Postnatal Control	15.15 ±0.29	15.15 ± 0.37	34.33 ± 0.80	2745.30 ± 39.87	155.20 ± 1.58	7.45 ± 0.29	43.70 ± 0.49	10.85 ± 0.29	4.70 ± 1.36.
Postnatal 2 mg/kg	23.12* ± 0.69	30.95* ± 0.33	49.83* ± 1.30	1595.80* ±12.04	165.20* ±3.11	21.30* ± 0.84	47.40 ± 1.09	11.903± 0.30	7.11* ± 1.44.

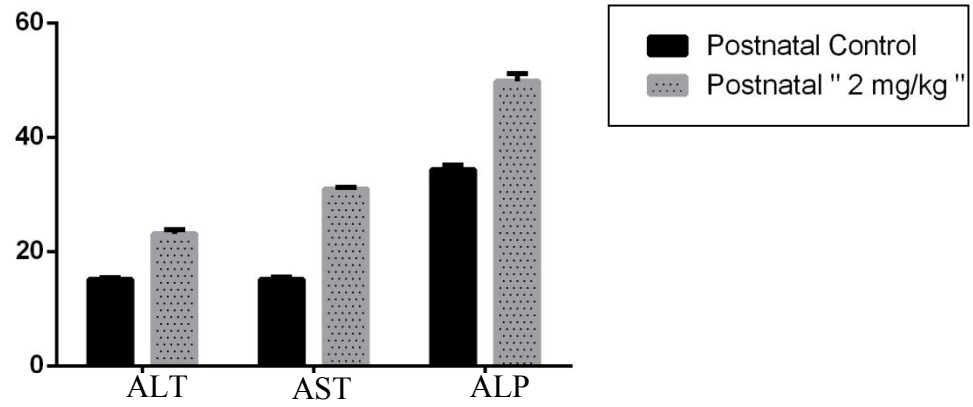

Fig.(12): ALT, AST and ALP values of foeti .

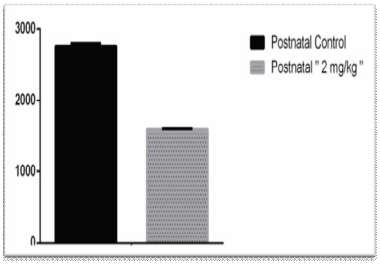

Fig.(13): GST values.

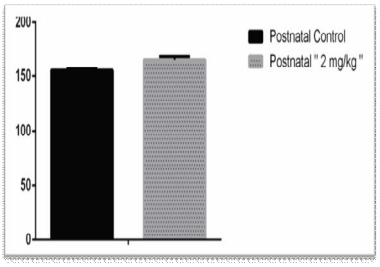

Fig.(14): SOD values.

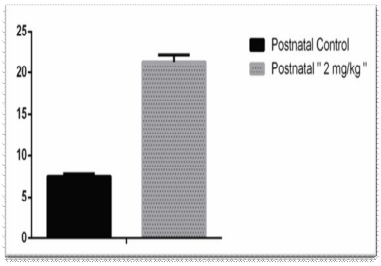

Fig.(15): NO values.

Histopathological changes

Histopathological examination of mother tissues indicated that liver tissues showed massive nercrosis around central vein. The kidney showed glomerulonephritis and degenerative changes in renal tubules (fig.16). Spleen showed Spleenitis, lymphoid depletion and hyperplasia of germinal center. Brain showed neuronal necrosis and astrocytosis. Histopathological examination of fetal tissues revealed that the liver showed chronic hepatitis with grade III fibrosis (fig.17). The kidney showed glomerulonephritis and swelling of renal tubules. Spleen showed necrosis of lymphocyte and congestion of splenic sinusoid. Brain showed neuronal necrosis with astrocytosis and demyelination, beside microgliosis and perivascular cuffing with lymphocytes. (fig.18).

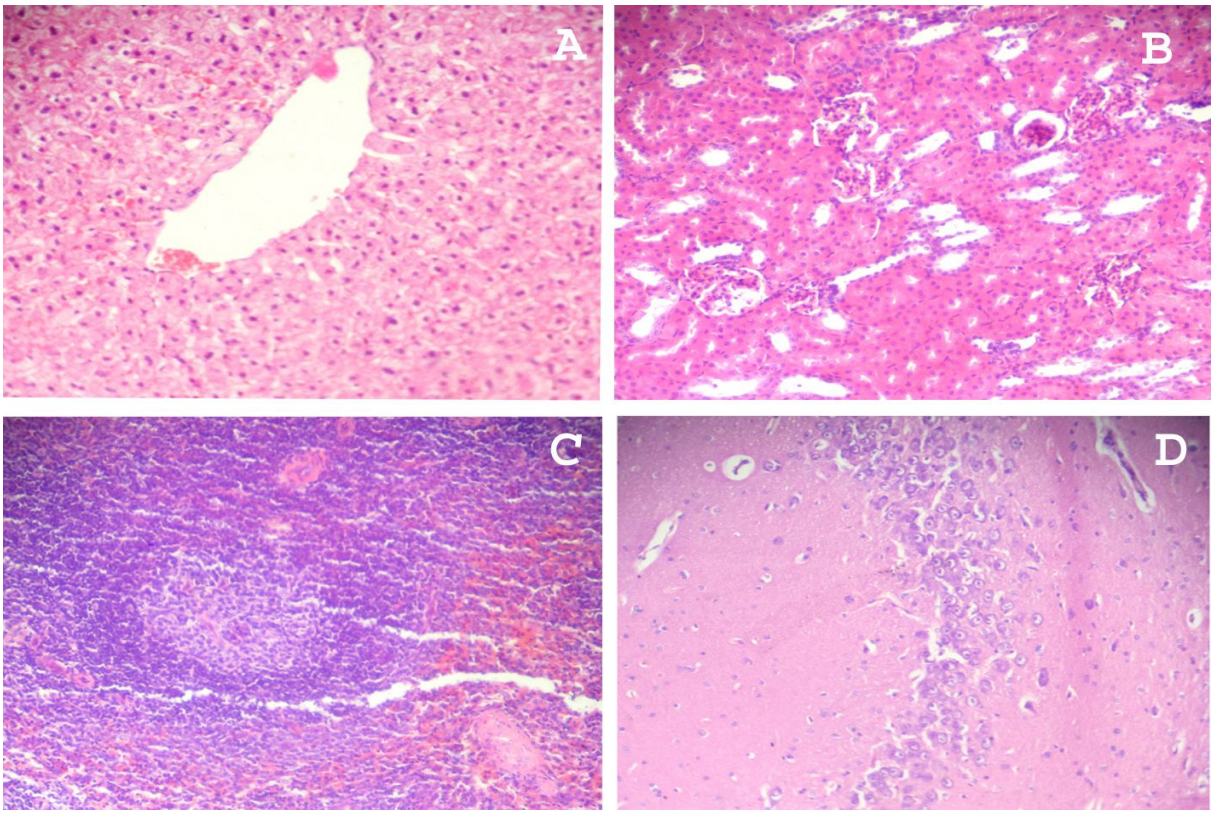

Fig. (16) Histopathological changes of mother tissues at 30th day postnatal received 2 mg\kg B.wt of abamectin,

a- Section from liver showing showed massive nercrosis around central vein. (10X).

b- Section from kidney showing glomerulonephritis and degenerative changes in renal tubules (10X).

c- Section from spleen showing Spleenitis, lymphoid depletion and hyperplasia of germinal center. (10X).

d- Section from brain showing neuronal necrosis and astrocytosis. (4X).

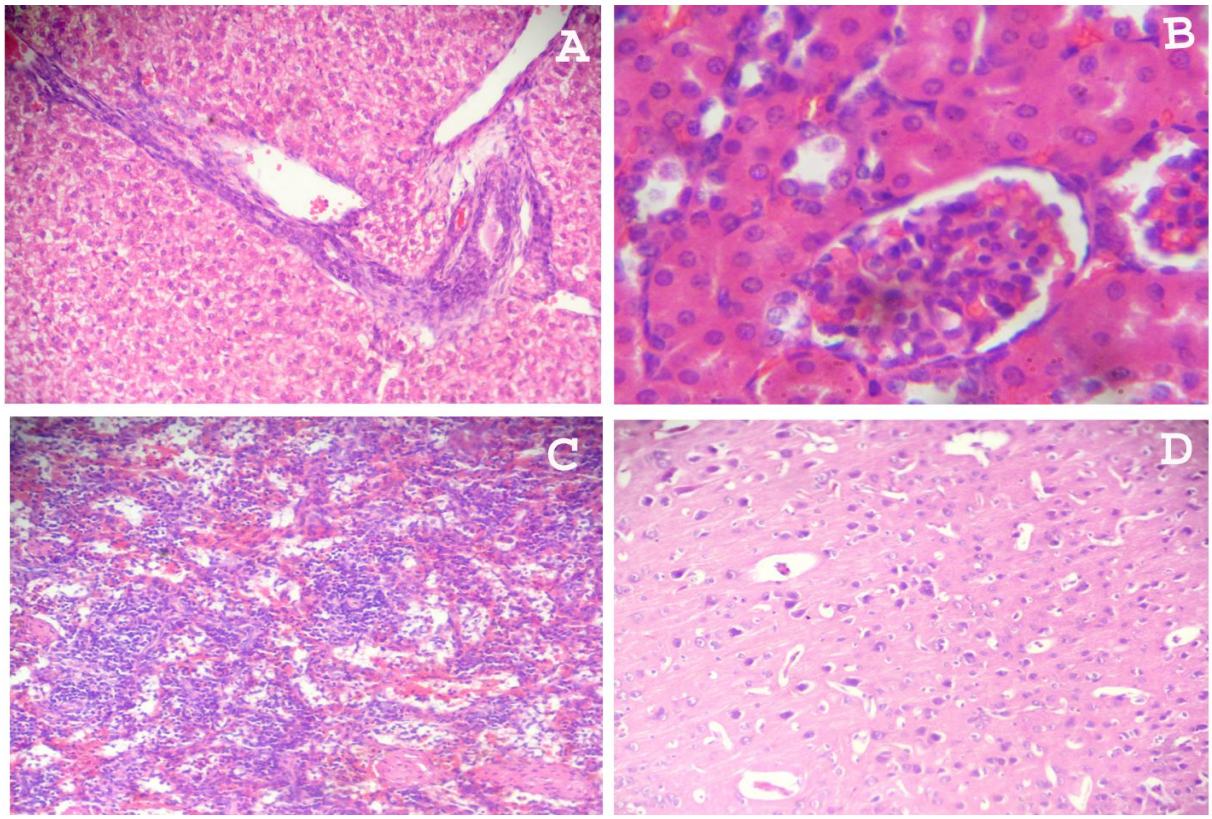

Fig. (17) Histopathological changes of suckling fetus's tissues at 30th day postnatal from mother received 2 mg\kg B.wt of abamectin,

a- Section from liver showing Chronic hepatitis with grade III fibrosis (arrow)(10X).

b- Section from kidney showing glomerulonephritis and swelling of renal tubules. (10X).

c- Section from spleen showing necrosis of lymphocyte and congestion of splenic sinusoid. (10X).

d- Section from brain showing neuronal necrosis with astrocytosis and demyelination, beside microgliosis and perivascular cuffing with lymphocytes (4X).

DISCUSSION

Pesticides are agricultural chemicals used for controlling pests on the plant or animals. Problems associated with pesticide hazards to man and environment are not confined to the developing countries, but extended to developed nations and still facing some problems in certain locations **(Nuckols *et al.*, 2007)**.

Abamectin administration caused a significant decrease in total leukocytic count (TLC) and PCV values. A significantly reduction in total count of white blood cells could be indicative of immune-suppressionm **(Schroder et al., 2007)**.The obtained results are in

agreement with those found by **Ali, (1990); Anubama et al., (2001)** who stated that avermectins reduced leukocyte counts in rabbits and rats.

Oral administration of abamectin significantly increased the activities of plasma AST and ALP in treated rabbits, compared to the control group. While, the activity of ALT not altered. These findings were in agreement with the results of **Hsu et al., (2001).** They indicated that the activity of AST level was elevated in abamectin in rats in a dose-dependent manner at 1, 3, and 12 h, respectively. Activity of serum enzymes like AST and ALT, represented the functional status of the liver **(Cremer and Seville, 1982).** As certain hepatic damage is considered pathologically irreversible (**Helling et al., 1995**), the elevation of AST may render the liver to be more susceptible to other toxicants **(Chamulitrat and Spitzer, 1996; Nayak et al., 1996).** Aspartate aminotransferase is an important indicator of liver damage in clinical studies. During hepatocellular injury, AST was found to be secreted into the blood **(Kalender et al., 2005).** In dying or damaged cells, these enzymes leak into the blood stream **(Mansour and Mossa, 2010).** However the results were disagreed with those of **Ewies et al., (1995**)and **Abd El-Wahab et al., (2002)** who found that abamectin caused a decrease in ALT and AST activities in rats. In addition, Gomes et al., (1999) revealed marked decrease in ALT and AST activities as a result of treatment with a mixture of organophosphorous pesticides.

Oral administration of abamectin induced a significant decrease in the activities of GST and SOD enzymes. The obtained results was in agreement with **El-Shafey et al., (2011)** due to that GST involved in detoxification of abamectin to non-toxic products or by rapidly binding and very slowly turning over the insecticide. Also, with **El-Shenawy, (2010)** who reported decreased GST activities in rat liver following exposure to insecticides fenitrothion, endosulfan and abamectin and the auther added that organophosphorous insecticides consume GSH through a detoxification reaction and that GST catalyzes this reaction between GSH and xenobiotic regulating possible harm **(Mulder et al., 1990)**. The present results are coincident with **El-Demerdash,(2011)** who reported that significant decrease in the antioxidant enzyme activity (GST) in liver proved the failure of antioxidant defense system to overcome the influx of reactive oxygen species generated. However, the inhibition of enzymes involved in free radical removal led to the accumulation of H_2O_2 which promoted lipid peroxidation, altered gene expression and cell death **(Halliwell and Gutteridge, 1999).** The decline in the enzyme activities may be due to an excessive formation of superoxide anions, thus resulting in an inactivation of H_2O_2 scavenging enzyme.

Abamectin caused a significant increase in the NO levels. This finding agree with (**Hsu et al., 2001**) where NO increased in rats orally given 1.5 to 20 mg\kg of ivermectin. On the other hand, our findings disagree with (**Zhang et al., 2009)** where 2µg\ml and 4µg\ml of ivermectin resulted in decrease in NO by 10% and 30% respectively at 24hr period in lipopolysaccharide treated RAW 264.7 cell culture model.

In the present study, there was a significant decrease of the body weight gain of the litter was recorded during lactation. The obtained results are agree with those of **Medeiros et al., (2008)** who reported that the treatment of female rats with ivermectin at doses of (0.5, 1, 2, 4, 8 and 10 mg\kg) increases the incidence of the estrus phase. In addition, a definite deleterious effect is exerted on nursing animals as revealed by reducing body weight gain of the litters. Also, these results are agree with those of **Wise et al.,(1997)** who reported a progressive decreases in preweaning average weights were observed in the high-dose group (3.6 mg\kg of Emamectin benzoeate)**.** Further studies using radiolabeled ivermectin indicated that high drug concentrations in the milk of exposed dams led to high drug levels in the plasma and brain of the offspring (relative to adult rats) and were probably responsible for the observed toxicity **(Lankas et al., 1989).**

In relation to the study of **Poul (1988),** which assessed preweaning pup parameters in rats following exposure to ivermectin during gestation and lactation, the results of this study show that abamectin is less toxic to the fetuses. In the study with ivermectin, dose levels of 2 and 4 mg/kg/day resulted in significant mortality before weaning whereas mortality occurred at abamectin dose levels up to 2 mg/kg/day administered during lactation.

The susceptibility of rabbit fetuses to the avermectins may be related to the levels of *P*-glycoprotein as suggested by work in mice. The sensitivity of mice to ivermectin neurotoxicity was shown to be due to the presence of a *P*-glycoprotein synthesized by the multidrug resistance gene *mdr1a* (**Schinkel et al., 1994**). Mice homozygous for a disruption of the *mdr1a* gene have no physiological, anatomical, or histological abnormalities but are 50- to 100-fold more sensitive to orally administered ivermectin than genetically matched *mdr1a* (*1*/*1*) mice. This increased sensitivity was correlated with a near absence of immunohistochemically detectable *P*-glycoprotein in the brains of these mice (**Schinkel et al., 1994**). More recently, our laboratory has shown that *P*-glycoprotein in brain capillary endothelia and intestine of rats is nearly absent at birth and reaches mature levels at about 5 weeks of age (**Lankas et al., 1996**).

REFERENCES

Abd El-Wahab I.; Eissa A.I.; Khalil S.M. and Hoda E. (2002): Effect of the biopesticide, abamectin on the liver and kidney functions in albino rats. *Egypt. J. Biochem.,* **20:** 183-195.

Ali B.H., (1990): The effect of ivermectin on some haematological indices in rabbits: influence of vitamin k treatment. Clin. Exp. Pharmacol. Physiol., 17: 735-738.

Anubama V.P., H. Honnegowda K. Jayakumar G. Krishnappa K. Narayana and Y.B. Rajeshwari, (2001): Effect of doramectin on immune response of rats to SRBC antigen. India Vet J., 78: 779-782.

Bancroff J.P.; Stevenes A. and Turner D.R. (1990) : Theory and practice on histological techniques, third edition, Clurechill Livingston, Edinburgh, London.

Belfield A. and Goldberg D.M. (1971) : A colorimetric method for determination of serum Alkaline Phosphatase enzyme 12, 561.

Campbell W.C., (1989): Ivermectin and Abamectin. Springer Verlag, New York.

Chamulitrat W., Spitzer J.J. (1996): Nitric oxide and liver injury in alcohol-fed rats after lipopolysaccharide administration. Alcohol Clin. Exp. Res. 20 (6): 1065–1070.

Coles E.H. (1986) : Veterinary clinical pathology. 4th Ed. W.B.Saunders Company, Philadelphia, 279-297.

Cremer J.E., Seville M.P. (1982): Comparative effects of two pyrethroids, deltamethrin and cismethrin on plasma catecholamines and on blood glucose and lactate. Toxicol. Appl. Pharmacol. 66 (1): 124–133.

Cully D.F., Vassilatis D.K., Liu K.K., Paress P.S., Van der Ploeg L.H.T., Schaeffer J.M., Arena J.P., (1994): Cloning of an avermectin-sensitive glutamate-gated chloride channel from Caenorhabditis elegans. Nature, 371.

Drabkin D.L. (1949) : Standarization of hemoglobin measurement in fish medicine Stockopf, K.M. (ed), 1st ed; W.B. Saunders Co. Philadeiphia. 114-115.

El-Demerdash F.M. (2011): Lipid peroxidation, oxidative stress and acetylcholinesterase in rat brain exposed to organophosphate and pyrethroid insecticides. Egypt Food and Chemical Toxicol., 49 (6): 1346-1352.

Elissa F.I. and Zidan N.A. (2010): Haematological, biochemical and histopathological alterations induced by abamectin and Bacillus Thuringiensis in male albino rats. J. of Basis & Applied Sci., 3 (3): 2497-2505.

El-Shafey A.A.M.; Selim M..E.; El-Mahrouky F.; Gabr W.M. and Kandil R.A.(2011): Some Physiological and Biochemical Effects of Oshar Extract and Abamectin Biocide on male albino rats. Journal of American Science,7(12) : 254-261.

El-Shenawy N.S. (2010): Effects of insecticides fenitrothion, endosulfan and abamectin on antioxidant parameters of isolated rat hepatocytes. J. Toxicol. In Vitro, 24 (4): 1148-1157.

El-Shenawy N.S. (2010): Effects of insecticides fenitrothion, endosulfan and abamectin on antioxidant parameters of isolated rat hepatocytes. J. Toxicol. In Vitro, 24 (4): 1148-1157.

Ewies E.; El-Hwashy N.; Said H. and Kandil M. (1995): Acute toxicity of ivermectin in laboratory animals. 1st Int. Conf. of Pest Control, Mansoura, pp. 89-95.

Feldman B.F.; Zinkl J.G. and Jain V.C. (2000) : Schalm's Veterinary hematology. Fifth Edition. Lippincott Williams and Wilkins. Canda; P.P. 1145-1146.

Fisher M.H., Mrozik H., (1992): The chemistry and pharmacology of avermectinas. Annu. Rev. Pharmacol. Toxicol. 32, 537–553.

Gomes J.; Dawodu A.; Lioyd O.; Revitt D. and Anilal S. (1999): Hepatic injury and disturbed amino acid metabolism in mice following prolonged exposure to organophosphorous pesticides. *Hum. Exp. Toxicol.*, **18(1):** 33-37.

Habig W. and Pabst M.; Jakoby W.J. (1974) : A UV method for determination of Glutathione-S-Transferase. Biol. Chem. (249), 7130-7139.

Halliwell B. and Gutteridge J.M.C. (1999): Glutathion in metabolism. In *Free Radical in Biology and Medicine*, edited by: Halliwell, B. and Gutteridge, J. M. C. 146-150. Oxford, UK: Claredon Press.

Helling T.S., Wogahn B.M., Olson S.A., Evans L.S., Reddy B.R., VanWay C. (1995): The effect of prostaglandin E1 on liver adenine nucleotides and cytoplasmic enzymes in a porcine model of normothermic hepatic ischemia. Hepatology 22 (5): 1554–1559.

Hsu D.-Z., Hsub C.-H., Huangc B.-M., Liu M.-Y., (2001): Abamectin effects on aspartate aminotransferase and nitric oxide in rats. Toxicology 165 (2–3), 189–193.

Kalender S., Ogutcu A., Uzunhisarcikli M., Acikgoz F., Durak D., Ulusoy Y., Kalender Y.(2005): Diazinon-induced hepatotoxicity and protective effect of vitamin E on some biochemical indices and ultrastructural changes. Toxicology 211 (3): 197–206.

Kovecses J., Marcogliese D.J., (2005): Avermectins: potential environmental risks and impacts on freshwater ecosystems in Quebec. Scientific and Technical Report ST-233E. Environment Canada – Quebec Region, Environmental Conservation, St. Lawrence Centre.

Lankas G. R.; Cartwright M.; Minsker D.; Cukierski M. (1996): Postnatal development of P-glycoprotein, a component of the blood– brain and intestinal barriers, in rats. Fundam. Appl. Toxicol. Suppl. 30:263.

Lankas G. R.; Minsker D. H.; Robertson R. T. (1989): Effect of ivermectin on reproduction and neonatal toxicity in rats. Food Chem. Toxicol. 27:523–529.

Lankas R.G. and Gordon L.R. (1989) : Toxicology. In : "Ivermectin and Abamectin" (Campbell. W.C., ed.) Springer Verlag. New York. NY., 10-142.

Mansour S.A., Mossa A.H. (2010): Oxidative damage, biochemical and histopathological alteration in rat exposed to chlorpyrifos and the role of zinc as antioxidant. Pest. Biochem. Physiol. 96 (1): 14–23.

Medeiros, J.P. Evencio, L.B. Simoes, R.S. Luz, L.E. Estevao, L.R.M. Simoes, M.J. and Neto, E. (2008) : Effect of treatment by Ivermectin on pregnancy and lactation periods of rats. Arg. Inst. Biol., Saopaulo, V. 74, N .1, P. 17-21.

Montgomery H.A.C and Dymock J.F. (1961) : A colorimetric method for determination of serum nitric oxide. Analyst, 86, 414.

Mulder G.J.; Adang A.E.P.; Brussee J.; Ketterer B.; Meyer D. and Van de Gen A. (1990): The Glutathione binding site of glutathione-s-tranferase isoenzymes from the rat: selectively towards tripeptide analogues of glutathione. Glutathione-S-transferase and drug resistance. Taylor and Francis, Great Britain. p. 75

Nayak N.C., Sathar S.A., Mughal S., Duttagupta S., Mathur M., Chopra P. (1996): The nature and significance of liver cell vacuolation following hepatocellular injury-an

analysis based on observations on rats rendered tolerant to hepatotoxic damage. Virchows Archiv. 428 (6): 353–365.

Nishikimi M.; Roa N.A. and Yogik (1972) : A colorimetric method for determination of serum Superoxide dismutase. Biochem. Bioph. Res. Common., 46, 849-854.

Nuckol, J.R.; Gunier R.B.; Riggs P.; Miller R.; Reynolds P. and Ward M.H. (2007). Linkage of California pesticide use reporting data-base spatial land use for exposure assessment. Environ. Health Perspect., 115 (5) : 684-689.

Poul J.M. (1988): Effects of perinatal ivermectin exposure on behavioral development in rats. Neurotoxicol. Teratol. 10: 267–272.

Reitman S. and Frankel S. (1957) : A colorimetric method for determination of serum ALT, AST. Am. J. Clin. Pathol., 28:56.

Schinkel A.; Smit J.; van Tellingen O.; Beijnen J.; Wagenaar E.; van Deemter L.; Mol C.; van der Valk M.; Robanus-Maandag E.; te Riele H.; Berns A.; Borst P. (1994): Disruption of the mouse mdr1a P-glycoprotein gene leads to a deficiency in the blood– brain barrier and to increased sensitivity to drugs. Cell 77:491–502.

Schrøder, M., M. Poulsen, A. Wilcks, S. Kroghsbo, A. Miller, T. Frenzel, J. Danier, M. Rychlik, K. Emami, A. Gatehouse, Q. Shu, K. Engel, I. Altosaar and I. Knudsen, (2007): A 90-day safety study of genetically modified rice expressing Cry1Ab protein (*Bacillus thuringiensis* toxin) in Wistar rats. Food Chem Toxicol, 45: 339–349.

Snedecor G.W. and Cochran W.G.(1984) : Statistical methods. 7th Ed., the Iowa state University Press, Ames. Iowa. U.S.A.

Wise, L.D. Allen, H.L. Hoe, C.L. Verbeke, D.R. and Gerson, R.J., (1997) : Developmental Neurotoxicity evaluation of the Avermectin pesticide, Emamectin benzoate in sprague-Dawly Rats. Neurotoxic. And Teratol., vol.19, No.4, pp. 315-326.

Zhang X.; Song Y.; Xiong H.; Zhang L.; Deng X. (2009): Inhibitory effects of ivermectin on nitric oxide and prostaglandin E2 production in LPS- stimulated RAW 264.8 macrophages. Int. Immunopharmacol; 9: 354-359.

الملخـــص العـــربي

سمية ما بعد الولادة لمادة الاباميكتين فى الارانب

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أجريت هذة التجربة لدراسة التأثير السمى للمبيد الحشرى الاباميكتين على كلا من الامهات و الولدات خلال فترة الرضاعة من خلال دراسة التغيرات فى كلا من فحوصات مصل الدم والدراسات الهستوباثولوجية لمختلف الاعضاء.

اجريت الدراسة على ١٢ انثى عشارنيوزيلندى تم تقسيمهم الى مجموعتين ٦ لكل مجموعة. المجموعة الاولى ضابطة وتم تجريعها ماء مقطروالمجموعة الثانية تم تجريعها ٢ مجم من الاباميكتين لكل كجم من وزن الجسم فى الفترة من اليوم الاول بعد الولادة حتى اليوم الثلاثين من الرضاعة.

وقد تم تسجيل اوزان الولدات كل اسبوع ولمدة شهربعدها تم ذبح الامهات والولدات بعد شهر من الرضاعة.و قد تم أخذ عينات الدم لفحص صورة دم كاملة و فصل مصل الدم وايضا اجراء الصفة التشريحية لكلا من الامهات و الولدات .

واسفرت النتائج عن الاباميكتين يسبب نقصان ملحوظا فى اوزان الولدات اثناء فترة الرضاعة.و ايضا يسبب زيادة ملحوظة فى انزيم الاسبارتيت امينو ترانسفيريز و الالكالين فوسفاتيز بينما يسبب نقص فى نشاط الجلوتاثيون اس ترانسفيريز و سوبر اكسيد ديسميوتيز فى الامهات . اما بالنسبة للولدات فكانت هناك زيادة ملحوظة فى عدد كرات الدم البيضاء و حجم الدم المضغوط و تركيز الهيموجلوبين الى جانب زيادة فى انزيمى الامينو ترانسفيريز و و الالكالين فوسفاتيزو سوبر اكسيد ديسميوتيز واكسيد التيتريك بينما نقص نشاط الجلوتاثيون اس ترانسفيريز.الدراسات الهستو باثولوجية اوضحت تغيرات مرضية فى الكبد والكلى والطحال والمخ لكلا من الامهات والولدات.

و قد خلصت الدراسة الى ان الاباميكتين له تأثير ضار على الامهات والولدات اثناء فترة الرضاعة فى الارانب.