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Effects of Ivermectin on some neurochemical parameters and histological changes in chicks

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Abstract

The study's goal was to detect the toxic effects of Ivermectin on the liver enzyme activity levels and the concentration of glutamate and glycine in the plasma in the histological section of the brain in chicks. The activity of liver enzymes and the concentration of glutamate and glycine in the plasma were measured as histological sections of the brain were taken after treating the chicks with Ivermectin at a dose of 131.5, 263.0 and 394.5 mg/kg orally after 24 hours of treatment, and the concentration of glutamate and glycine was measured after 5 days of Ivermectin treated at 26.3, 52.6 and 105.2 mg/kg orally .Ivermectin had no toxic effect on the activity of liver enzymes, but its activity was within the normal range in poultry. Ivermectin at doses 131.5, 263, and 394.5mg/kg caused a significant decrease in the plasma concentration of glutamate, while the concentration of glycine was insignificant. Ivermectin had a moderately toxic and rapid effect on the brain through the presence of edema, infiltration of inflammatory cells, vacuolar degeneration of neurons, and their size shrinkage. The dose of 26.3 mg/kg caused a significant decrease in glutamate concentration companies and a significant increase in glycine concentration. The results proved that Ivermectin has a safe effect on the liver by not affecting its enzymes, and it has a moderately toxic effect on the brain tissue represented by (edema, infiltration of inflammatory cells, and vacuolar degeneration), in addition to its effect on the concentration of glutamate and glycine in the plasma.

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Introduction

Ivermectin belongs to the family of avermectins and is isolated from fermentation products of *Streptomyces avermetilis* in the first place (1-3). Ivermectin acts as an anti-parasitic drug through its sensitive effect on glutamate-gated Cl^- channel receptors in some invertebrates and GABA receptors. Ivermectin can cause side effects through its effect on GABA release or its action as an agonist of GABA receptors; it increases chloride conduction (4,5). Ivermectin interacts with at least three targets in the mammalian central nervous system, including GABA-dependent chloride channels, glycine-dependent chloride channels, and voltage-dependent chloride channels (6,7). Neurotransmitters are essential in transmitting information and nerve signals, acting as messengers in the chemical synapses (8). Neurotransmitters of amino acids are distributed in the central nervous system, especially the brain and cerebrospinal fluid. In general, neurotransmitters can be divided into two categories: excitatory amino acids, such as glutamate and aspartate, and inhibitory amino acids, such as GABA and glycine. The amino acid neurotransmitter receptors influence synaptic transmissions, such as the senses, and information delivery in the nervous system. The level of amino acid neurotransmitters in the brain changes significantly after injury, as it causes an imbalance in the excitatory and inhibitory neurotransmitters (8,9). Previous research indicated that Ivermectin enhances the secretion of

GABA, and its binding to the receptor result in Cl^- influx, hyperpolarization of the cell membrane causes inhibition of neural cells (9). Ivermectin also induces the opening of glycine-gated chloride channels, which works to open chloride channels, increase membrane permeability to chloride, and reduce nerve conduction, which leads to apoptosis, excitotoxicity, and necrosis (10,11).

Previous studies clarified the role of Ivermectin in regulating neurotransmitters and their receptors in vertebrates, but they were not well elucidated in poultry. Therefore, our current study aimed to explore the toxic effects of Ivermectin on the liver enzyme activity and the activity of neurotransmitters such as glutamate and glycine in the blood plasma, in addition to studying the histological changes caused by acute ivermectin poisoning in chicks.

Materials and methods

Ethical approve

We obtained the official approval for the study design from the committee of postgraduate studies at the College of Veterinary Medicine, University of Mosul, Iraq, according to institutional regulation on animal handling and used in study. UM.VET.2021.47.

Animals

This study used broiler chicks Rose type obtained from local hatchers in Mosul. Chicks were brought at one day old from hatching and lived under standard environmental conditions of temperature, humidity, and light. The chicks were fed and watered daily and placed in special cages belonging to the animal house in the College of Veterinary Medicine, University of Mosul.

Drug preparation

The pure powder of Ivermectin was obtained from Pioneer Company, Sulaymaniyah, Iraq. The required doses were prepared in the experiments by dissolving Ivermectin in propylene glycol (99%, Sigma Chemicals, USA), and the administration volume was 5ml/kg of body weight.

Effect of toxic doses of ivermectin on enzyme activities, glutamate and glycine concentrations in plasma, and histological changes in the brain

Twenty-four chicks weighing 55-65 g at 7 days of hatching age were divided randomly into four groups. Each group included six chicks. The first group was a control group treated with propylene glycol with an administration volume of 5 ml/kg of body weight. The remaining three groups were treated with Ivermectin orally at doses131.5, 262.9, and 394.5 mg/kg of body weight, respectively.

Biochemical analysis

After 24 hours of treatment, blood samples were drawn from the jugular vein in the neck and collected by a heparinized test tube. The plasma was separated using a centrifuge at 3000 rpm for 15 minutes. The samples were collected in Eppendorf tubes and then kept freezing at a temperature of 18-º until tests were performed the next day. Enzyme activity measurements (AST, ALT, and ALP) were done using standard kits for each test (BIOLABO SA, Maizy, France). All parameters were analyzed using a spectrophotometer (EMLAB, Germany) (12,13).

Neurobiochemical study

The collected plasma samples were used to measure the concentration of the neurotransmitters glutamate and glycine using kits (ELK Biotechnology, Wuhan, China). The results were analyzed using ELISA (Paramedical, PKL, Italy).

Histopathological study

After 24 hours of treatment ,the whole brain was extracted and placed in buffered formalin solution at a concentration of 10% for 72 hours for histological examination. Tissue slices at 5 micrometers thick were made using a microtome device, and then the slices were stained with hematoxylin-eosin (14,15). Then the sections were examined under a light microscope, and images were taken using a digital camera (HDCM-5).

Effect of repeated doses of Ivermectin on the concentration of the neurotransmitter's glutamate and glycine in the plasma of chicks

Twenty-four chicks, whose weight ranged between 60-75 grams and 7 - 12 days old, were randomly divided into four groups. Each group included six chicks. The first group was controlled and treated with propylene glycol orally, administered with a volume of 5 ml/kg of body weight, for five consecutive days, starting from the seventh day of age, and the remaining three groups were treated with Ivermectin orally at doses 26.3, 52.6 and 105.2 mg/ kg of body weight, respectively. On the sixth day of dosing, blood was collected from the jugular vein in the neck and collected in the heparinized test tube, and the plasma was separated using a centrifuge. The samples were kept in Eppendorf tubes and kept freezing at a temperature of -18ºC until tests were carried out the next day.

Statistical analysis

Our data was statistically analyzed using (ANOVA) one-way analysis using SPSS software version 16, followed by the LSD analysis, the level of significance was at $P \leq 0.05$.

Results

Ivermectin doses at 131.5, 263, and 394.5 mg/kg body weight had no significant effect on enzyme activity, as the two doses 131.5 and 394.5 mg/kg led to a slight increase in the AST activity compared to the propylene glycol group (control group). In contrast, the Ivermectin at doses of 131.5,

263, and 394.5 mg/kg led to a slight decrease in the ALP activity compared to the propylene glycol group (Table 1).

Neurobiochemical study

Oral administration of Ivermectin at doses 131.5,263 and 394.5 mg/kg of body weight caused a significant decrease in the concentration of glutamate in the plasma of chicks compared with the control group treated with propylene glycol (Figure 1), this was accompanied by a non-significant decrease in the concentration of glycine caused by the dose of Ivermectin 394.5mg/kg, (Figure 2).

Table 1: Effect of Ivermectin on the liver function in chicks

Treated groups	Mean ± slandered error for 6 chicks /group		
	ALT (IU)	ALP (IU)	AST (IU)
Control (propylene glycol)	30.63±1.32	5.44±0.39	36.43±1.42
Ivermectin 131.5 mg/kg oral	31.12±2.09	4.39±0.62	49.70±8.09
Ivermectin 263 mg/kg oral	32.30±1.57	4.72±0.53	29.78±9.83
Ivermectin 394.5mg/kg oral	31.43±0.89	4.25 ±0.91	40.68±9.35

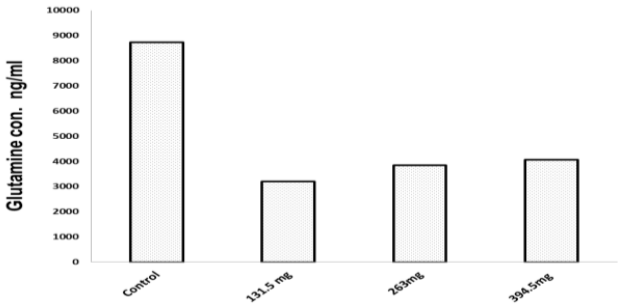

Figure 1: Glutamate concentration in the plasma of chicks treated with Ivermectin.

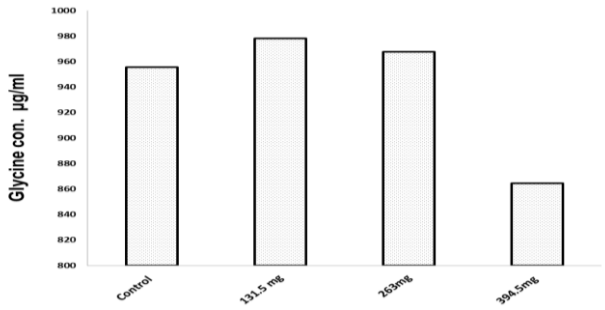

Figure 2: glycine concentration in the plasma of chicks treated with Ivermectin.

Histological examination

The brain of chicks treated with Ivermectin at 131.5 mg/kg body weight orally, after 24 hours of dosing, suffered from histological changes, including edema and infiltration of inflammatory cells and glial cells, as well as congestion of the blood vessels in the choroid plexus (Figures 3-5). Histology of the brain treated with Ivermectin at a dose of 263 mg/kg orally (Figures 6 and 7), the presence of edema and congestion around the blood vessels, shrinkage, and small size of a neuronal cell body, and vacuolar degeneration of neuronal and astrocyte cells. Brain treated with Ivermectin at a dose of 394.5 mg/kg shows the presence of edema, cells in white matter, and vacuolar degeneration in the neurons, in addition to the infiltration of oligodendroglia cells (Figure 8).

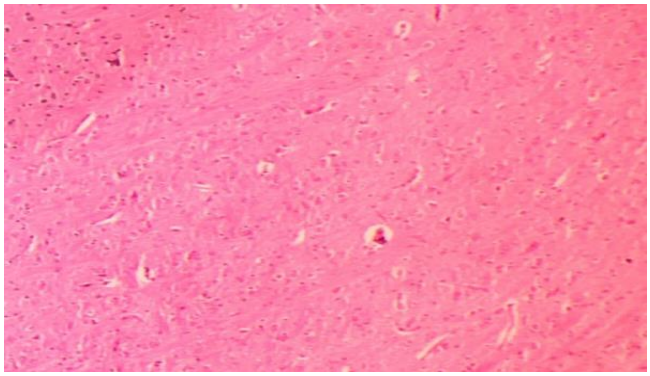

Figure 3: Brain histology of chick treated with propylene glycol control group. H&E, 40x.

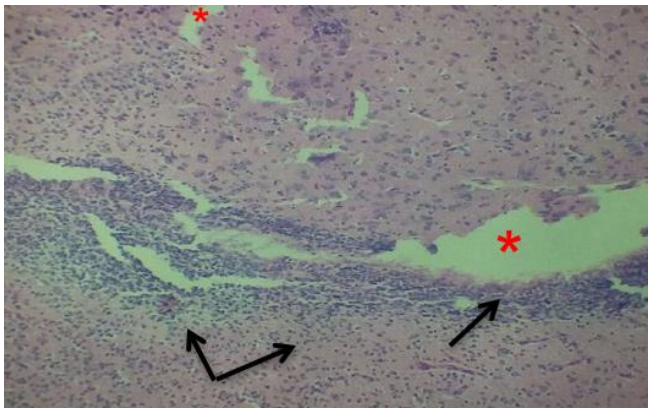

Figure 4: brain histology of chicks treated with Ivermectin at 131.5mg/kg orally after 24 h. of treatment show (*) edema, (arrow) infiltration of inflammatory cells, (two arrows) infiltration of glial cells. H&E, 150x.

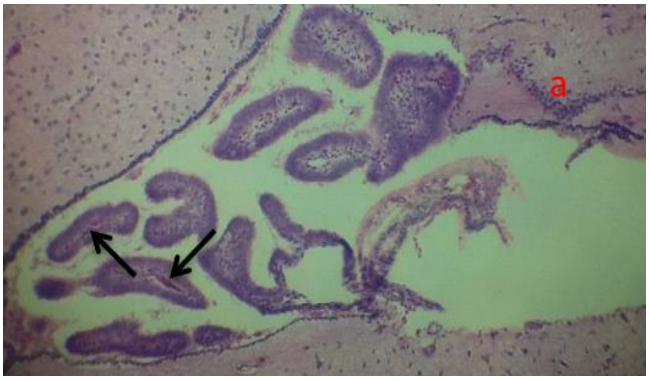

Figure 5: brain histology treated with Ivermectin 131.5 mg/kg orally after 24 h. show (arrow) congestion of the blood vessels in the choroid plexus and infiltration of inflammatory cells. H&E, 190x.

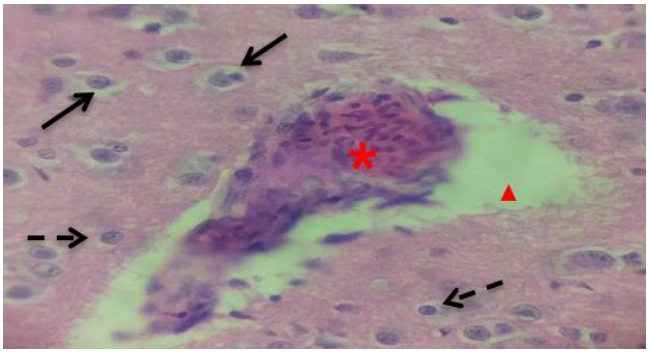

Figure 6: brain histology treated with Ivermectin 263 mg/kg orally after 24h. Show (*) congestion, (▲) Edema around blood vessels, (arrow) vascular degeneration of neurons, (segmented arrow) and astrocyte cells. H&E, 60x.

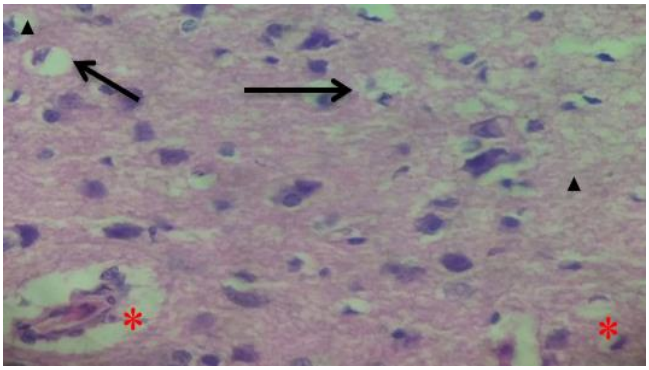

Figure 7: brain histology treated with Ivermectin 263mg /kg orally after 24h shows (*) edema around blood vessels, (▲) shrinkage and small size of neuronal cells, (arrow) vascular degenerative. H&E, 70x.

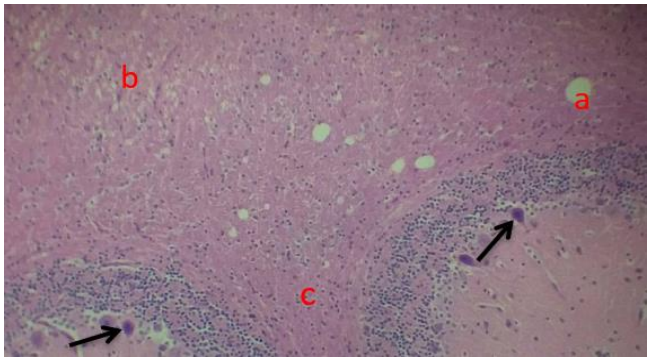

Figure 8: brain histology treated with Ivermectin 394.5 mg/kg orally after 24h show (a) white matter, (b) vascular degenerative of neurons, (c) infiltration of oligodendroglia, (*) edema. H&E, 210x.

Effect of repeated doses of Ivermectin on the concentration of the neurotransmitter's glutamate and glycine in the plasma of chicks

Oral administration of Ivermectin at a dose of 26.3 mg/kg for five consecutive days led to a significant decrease in the concentration of glutamate in the plasma of chicks compared to the control group (Figure 9). This was accompanied by a significant increase in glycine concentration in the plasma of chicks (Figure 10).

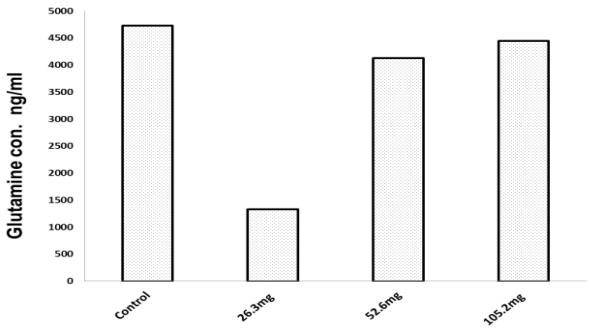

Figure 9: Glutamate concentration in the plasma of chicks treated with Ivermectin for 5 days.

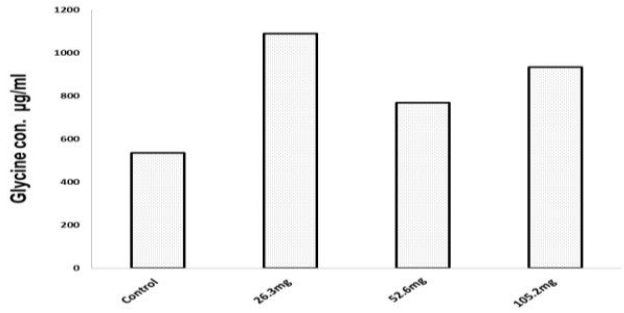

Figure 10: glycine concentration in the plasma of chicks treated with Ivermectin for 5 days.

Discussion

To determine some of the biomarkers that are affected by the toxicity in chicks, we performed some biochemical measurements, which included measuring the activity of the AST, ALT, and ALP. Our results indicate that chickens' liver enzyme concentrations are within the normal range (16,17). The histological changes of the brain indicated by our current results were of moderate severity and rapid occurrence as a result of exposure to high doses of Ivermectin, which were represented by edema, infiltration of inflammatory cells, and vacuolar degeneration (18-20) in rabbit and pigeon. The neurotoxic effect of Ivermectin is due to its effect on the GABA receptors, which affects the energy production of neurons, causing anaerobic respiration to produce energy, which causes an accumulation of lactic acid in the neurons leading to acidosis and cell destruction related to inflammation (18,19).

Glycine is one of the depressing neurotransmitters in the central nervous system, but it is less critical than GABA (21,22) and exerts its effects by binding to its receptors (21). Activation of the GABA and glycine receptors leads to chlorine influx, hyperpolarization of the cell membranes, and depressant effects on the central nervous system (21,23). The neurotoxicity of Ivermectin is related to the amino acid neurotransmitters in birds and vertebrates (24). In the animal's brain, glutamate is one of the excitatory calcium-dependent neurotransmitters, and its effect appears by binding to receptors, including NMDA and non- NMDA (24,25). It is essential in regulating ionic balance (25-28), membrane polarization, nervous excitatory, neurodegeneration, and death (29-32).

The current results showed a significant decrease in glutamate concentration after treatment with Ivermectin after 24 hours. On the other hand, treatment with Ivermectin for five consecutive days led to a decrease in glutamate and an increase in glycine in the blood plasma of chicks. The results here agree with previous studies about increasing the content of glycine and glutamate in pigeons' brains (23). This is due to the concentration of Ivermectin in the brain at a higher rate than its presence in plasma (28). Our results, on the other hand, disagree with previous studies about the increase in the concentration of glycine and glutamate in the brain of birds after 30 days of treatment with Ivermectin. A study referred to the increased concentration of neurotransmitters in the brain depending on the dose and time after 30 days of treatment (23). This is because the concentration of Ivermectin in the brain is higher than its concentration in the plasma (28). Previous results showed that ivermectin toxicity induced brain tissue injury and extensive membrane depolarization lead to excessive excitatory amino acid release, blocked reuptake, and obvious neurotoxicity (33-40).

Conclusions

The results proved that Ivermectin has a safe effect on liver function by non-affecting its enzymes (AST, ALT, and ALP). Moreover, it has a moderately toxic effect on the brain tissue (edema, infiltration of inflammatory cells, and vacuolar degeneration), in addition to its effect on the concentration of neurotransmitters (glutamate and glycine) in the blood plasma of chicks treated with Ivermectin.

Conflicts of interest

The researchers have no conflict of interest.

Acknowledgment

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تأثير الايفرمكتين على بعض المؤشرات الكيموعصبية والتغييرات النسجية في الأفراخ

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الخلاصة

كان الهدف من هذه الدراسة هو الكشف عن التأثيرات السمية للإيفرمكتين على مستوى نشاط إنزيمات الكبد، وتركيز الكلوتاميت والكلايسين في بلازما الدم والتغييرات النسجية الحاصلة في دماغ الأفراخ. تم قياس نشاط إنزيمات الكبد وتركيز الكلوتاميت والكلايسين في بلازما أفراخ وبعدها تم أخذ مقاطع نسيجية من الدماغ بعد معاملة الأفراخ بالإيفرمكتين بجرعة ١٣١,٥ و ٢٦٣ و ٣٩٤,٥ ملغم / كغم عن طريق الفم بعد ٢٤ ساعة من المعاملة، وتم قياس تركيز الكلوتاميت والكلايسين بعد إعطاء الإيفرمكتين لمدة خمسة أيام متتالية عن طريق الفم بجرع ٢٦,٣ و ٥٢,٦ و ١٠٥,٢ ملغم /كغم. لم يكن للإيفرمكتين أي تأثير سام على نشـــاط إنزيمات الكبد، لكن نشاطه كان ضمن المعدل الطبيعي في

الدواجن، بينما تسبب الإيفرمكتين بجرع ١٣١,٥ و ٢٦٣ و ٣٩٤,٥ ملغم / كغم في انخفاض معنوي في تركيز الكلوتاميت، في حين لم يكن الانخفاض معنويا في تركيز الكلايسين. كان للإيفرمكتين تأثير معتدل السمية على الدماغ من خلال وجود الوذمة، وارتشاح الخلايا الالتهابية والدبقية. تسببت الجرعة ٢٦,٣ ملغم/كغم بعد ٥ أيام من المعاملة الى انخفاض معنوي في تركيز الكلوتاميت مصحوبة بارتفاع معنوي في تركيز الكلايسين. أثبتت النتائج أن للإيفرمكتين تأثير آمن على الكبد من خلال عدم التأثير على إنزيماته، وله تأثير معتدل السمية على أنسجة الدماغ ممثلة في الوذمة، ارتشاح الخلايا الالتهابية والتنكس الفجوي، بالإضافة إلى تأثيره على تركيز الكلوتاميت والكلايسين في بلازما الدم بشكل متعاكس بعد ٥ أيام من معاملة الأفراخ.