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Acute toxicity events of ivermectin in chicks' model

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Abstract

Ivermectin is a very safe drug; however, there are many studies on its toxic effects in different animals due to sensitivity, misuse, or accidental overdose. This study aimed to further characterize the neurotoxic effects of ivermectin in chicks and identify possible therapeutic strategies for use in cases of ivermectin toxicity. The LD_{50} of ivermectin was determined by the Dixon method. The acute toxicity signs of ivermectin were induced at doses of 131.5,2629 and 394.5 mg/kg orally. The therapeutic effect of flumazenil on ivermectin poisoning was also studied. Administration of repeated doses of ivermectin for five consecutive days was recorded to measure the neurobehavioral within the open field and tonic immobility test. The oral LD_{50} of ivermectin was 525.9mg/kg. The acute signs of poisoning on ivermectin-treated chicks were lethargy, ataxia, tremor, diarrhea, recumbency, and death. Flumazenil at a dose of 0.1mg/kg significantly reduced the toxicity signs induced by the ivermectin in chicks, especially tremor and ataxia, and prevented death. The administration of ivermectin at 26.3, 52.6, and 105.2 mg/kg doses led to a significant decrease in motor activity through a significant increase in the time of starting the movement and a decrease in the number of cross lines. We concluded that ivermectin has a neurotoxic effect in chicks when used in high doses; the results also indicate a potential clinical application of flumazenil for treatment side effects and toxicity of ivermectin, as well as ivermectin, has depressant effect in chicks represented by open-field activity.

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Introduction

Ivermectin is one of the classes of compounds called avermectins. They are macrocyclic lactones produced by soil-dwelling bacteria *Streptomyces avermitilis* (a type of actinomycetes). It was approved for the first time for use in animals in 1981 (1-4). Ivermectin is used in veterinary medicine to treat parasitic infections in cattle, cats, dogs, and horses. Ivermectin exerts its anti-parasitic activity through its high ability to bind to glutamate channels, and GABA is found in invertebrates but not invertebrates. Binding to these receptors located in muscles and nerve cells of worms leads to an increase in the entry of chloride ions to the cells and resulting in paralysis and death of the parasite (5-8). Some studies prove the action of ivermectin on new sites of GABA receptors, which works to strengthen these receptors (9,10). Ivermectin does not cross the blood-brain barrier easily due to P-glycoprotein pumps located on the blood side of the cells lining the blood-brain barrier. Any ivermectin that reaches the cell is expelled directly to the outside by these pumps, except for ivermectin from the central nervous system because it is not easily crossed and does not cause neurological damage (11-13). Neurotoxic effects occur in cases including a mutation in the P-glycoprotein pump, which makes it unable to pump ivermectin out of the central nervous system, as is the case in Collies dogs when high doses of ivermectin are taken in cases of misuse and accidents, which works to flood the pump and allow

ivermectin to reach to the brain (14,15). The main concern is neurotoxicity, which manifests as systemic depression and ataxia that might be expected from inhibitory GABA ergic synapses (16-18). Flumazenil, an imidazobenzodiazepine, rapidly initiates its action following administration via placements. Its affinity is in α and γ2 subunits of GABA receptors. This is near the benzodiazepine binding site (19-22), where the α1 receptor controls sedation and muscle relaxation (23-25). The α2 or α3 anxiolysis and anticonvulsant affect the extrasynaptic receptor with α5 amnesia (26-28).

Limited studies are available on the poisoning profile of ivermectin in the avian species. Thus, the goal of this study was to clarify the neurotoxic effects of ivermectin in model chicks and to identify possible therapeutic strategies for use in cases of ivermectin toxicity.

Materials and methods

Ethical approve

According to institutional regulations on animal handling and use in research, we obtained official approval for the study protocol from the Committee of Postgraduate Studies at the College of Medicine, University of Mosul, Iraq. UM. VET. 2021.36.

Animals

Rose-type chicks of both sexes with one day age, obtained from local hatcheries in Mosul, were used in this study. The chicks were raised in standard conditions and provision of water, feed, litter, ventilation, and other breeding requirements from the animal house of the College of Veterinary Medicine, University of Mosul.

Doses of the drugs used

Ivermectin was used as a pure powder produced by the Pioneer Company, Sulaymaniyah, Iraq .The required doses of ivermectin were prepared by dissolving the equal weight of ivermectin in propylene glycol (99%, Sigma Chemicals, USA), and the volume of the given dose was 5 ml/kg of body weight. Flumazenil (0.1mg/ml, Mylan, France, SAS).

Determination of Acute LD_{50} of ivermectin

Nine chicks aged 7-14 days were used, their weights ranged between 46-83 g, and the initial dose of ivermectin was determined at 1000 mg/kg of body weight based on pilot experiments. One chick was taken and dosed at a dose of 1000 mg/kg of body weight, and the final result (the animal's death or survival) was read after 24 hours of dosing. The amount of increased and decreased lateral dose was a fixed amount of 100 mg/kg of body weight and by repeating this process with the change in the amount of dose until the change in the result (the survival or death of the animal) and after the appearance of the first change, then feeding three chicks individually, taking into account the change in the dose by ascending or descending, and according to the table mentioned by Dixon (29).

Effect of acute toxicity in chicks using different toxic doses of ivermectin

Twenty-four chicks were used, with weights ranging from 128 to 205 g and from 7-14 days of age from hatching age. All chicks were treated by oral dosing. The chicks were divided into four groups for each group of 6 chicks. The first group: The control group was given propylene glycol only . In the second, third, and fourth groups, the chicks were dosed with ivermectin at a dose of 131.5, 262.9, and 394.5 mg/kg of body weight, representing 25%, 50%, and 75% of the median lethal dose. The chicks were monitored immediately after dosing, and the signs of acute poisoning appeared on chicks. The start time of each sign was recorded, and the scores of poisonings for each group (30).

The therapeutic effect of flumazenil on chicks poisoned by ivermectin

Twenty-four chicks, whose weight ranged between 84-151 grams, were randomly divided into four groups. Each group included six chicks. The first and third groups were given a dose of ivermectin 262.9 and 394.5mg/kg orally, representing 50% and 75%, respectively, then injected with normal saline at 5ml/kg body weight i.p. At the same time, the second and fourth group was given a dose of ivermectin 262.9 and 394.5 mg/kg orally and then injected with flumazenil at dose 0.1mg/kg i.p (31) immediately after the appearance of complete signs of poisoning such as salivation, tremor, ataxia, lethargy, and death. The chicks were monitored in all groups for 2 hours after injection, and the signs of poisoning were recorded. The chicks were observed in terms of their death or survival after 24 hours of injection (32).

Effect of repeated doses of ivermectin for five consecutive days on the open field activity and tonic immobility test

In this experiment, 24 chicks were randomly divided into four groups with six chicks. The chicks were dosed with ivermectin (propylene glycol, 26.3, 52.6, and 105.2mg/kg orally), representing 5, 10, and 20% daily for five consecutive days. On the sixth day, the open-field box test was conducted in an isolated and quiet room. Each chick was subjected to an immobility test (33-35).

Statistical analysis

Frequency data were analyzed using the Fisher test, the data were analyzed using the one-way ANOVA test, and then the significance was worked out via the least significant test. The Man Whitney test was used to analyze non-parametric data using significance level at $P<0.05$ (36).

Results

The oral LD_{50} of ivermectin in chicks was 525.9 mg/kg. Chicks treated with ivermectin showed symptoms of toxicity during a period ranging between 20-30 minutes after dosing, Ruffled Feather, Closing Eyelid, lethargy with immobility, Drooping of the Head, Ataxia, tremor, Recumbency, salivation, diarrhea, paralysis and death (Table 1).

Effect of acute toxicity in chicks using different toxic doses of ivermectin

Oral administration of ivermectin in doses of 131.5, 262.9 and 394.3 mg/kg resulted in a significant decrease in the time of signs of toxicity compared with the control group, and appearance signs of poisoning were salivation, lethargy, tremor, ataxia, and diarrhea in different proportions ranging from 17-100% compared with the control group and. The poisoning scores were 18, 26, and 28 (Table 2).

The therapeutic effect of flumazenil in chicks treated with toxic doses of ivermectin

Dosing chicks with ivermectin at a dose of 262.9 and 349.5 mg/kg of body weight causes appearance signs of poisoning, salivation, ataxia, tremors, lethargy, and diarrhea, in addition to recumbency and death at a ratio, reach to 50-100 %. In contrast, flumazenil injection at a dose 0 and 1 mg/kg IP immediately after the full signs of poisoning appear causes a complete absence of signs poising with death prevention after 24 hours by a ratio reach to 33 and 67% (Table 3).

Effect of repeated doses of ivermectin for five consecutive days on the weight of chicks

Dosing chicks with ivermectin for five consecutive days at doses of 26.3, 52.6, and 105.2 mg/kg causes a significant decrease in chick weight compared to the control group 112.5 ± 4.20, and means at 91.17 ± 1.49, 80.17±3.22, 82.83±1.68 respectively.

Table 1: The oral LD_{50} of ivermectin in chicks for 24 hours by dixon approach

LD_{50} of ivermectin	525,9 mg/kg orally
Range of doses of ivermectin	1000-500= 500 mg/kg
The First dose	1000 mg/kg
The Last dose	600 mg/kg
Up and down ivermectin dose	100 mg/kg
Number of chicks	9 (xxxxxoxox)
Symptoms of poisoning in chicks	Lethargy with immobility, diarrhea, tremor, recumbency, and death.
The onset of poisoning symptoms	20-30 minute

*X = died of the chick; O = survived of the chick.

Table 2: Percentages of poisoning signs induced by ivermectin at doses 131.5, 262.9 and 394.5 mg/kg orally

Parameters	mean ± SE (6 chicks /group)			
	Control	131.5 mg/kg	262.9 mg/kg	394.5 mg/kg
The onset of poisoning signs (min.)	81.83±7.33	47.50±5.28*	28.67±5.55*	20.33±4.88*
lethargy and immobility%	0	100*	*100	*100
Ataxia %	0	17	50*	83*
Diarrhea %	0	50*	100*	100*
Tremor %	0	67*	100*	100*
Salivation %	0	0	50*	100*
Feather with close eyelids %	50	100*	100*	100*
Recumbency %	0	0	50*	50*
Score toxicity	2	18	26	28

*Significantly dissimilar from the control group at $P<0.05$.

Table 3: Therapeutic effect of flumazenil in chicks treated with toxic doses of ivermectin

Doses mg/kg	Onset (min)	Diarrhea %	Ataxia %	Tremor %	Salivation %	Lethargy %	Death (h)
Ivermectin 262.9 orally +normal saline. i.p	26.5±5.16	100	100	100	50	100	33
Ivermectin 262.9 orally+ flumazenil (0.1) i.p	0.00±0.00	0*	0*	0*	0*	0*	0
Ivermectin 394.5 orally + normal saline i.p	21.5±1.20	100	100	100	100	100	67
Ivermectin 3 94.5orally + flumazenil (0.1) i.p	0.00±0.00	0*	0*	0*	0*	0*	0

Values mean ± SE for 6 chicks/group. *Significantly dissimilar from the groups treated with ivermectin at 262.9 and 394.5 mg/kg at $P<0.05$.

Effects of repeated doses of ivermectin on the open-field activity

Dosing chicks with ivermectin at repeated doses for five days 52.6, 105.2 mg/kg led to a significant decrease in motor activity and neurobehavioral in the open field within 3 minutes through a significant increase in the time of movement start and a decrease in the number of cross lines in addition to a significant increase in the time of tonic immobility test (Table 4).

Table 4: Effects of repeated doses of ivermectin on the open-field activity (3 min)

Parameters	mean ± SE (6 chicks /group)			
	Control group	26.3 mg/kg	52.6 mg/kg	105.2 mg/kg
The onset of movement (min)	19.83±3.95	34.67±7.82	63.33±11.82*	69.50±7.67*
Lines cross	4.17±1.25	2.33±3.26	1.33±1.37	1.00±0.45*
Number of defecations	1.00±0.00	0.50±0.22	0.83±0.31	0.00±0.00*
Jumping number	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
Voices of score	1.00±0.00	0.50±0.22	0.50±0.22	0.50±0.22
Pecking number	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
Tonic immobility test (min)	32.17±4.29	53.17±4.83	115.83±13.95*a	73.67±4.88*

*Significantly dissimilar from the propylene glycol treated group (control group) at P<0.05. Significantly dissimilar from the 26.3 mg/kg ivermectin treated group 5% of LD_{50} at P<0.05.

Discussion

Ivermectin has a wide margin of safety and ease of administration. It is widely used in domestic animals, poultry, rodents, and the human field. Our current results recorded for the first time that the oral LD_{50} of ivermectin in chicks was 525,9mg/kg orally, in the rest of the animal species, where it was in mice 20.9 mg/kg orally (37) and in rats was 51.5 mg/kg s/c (38), in dogs 80 mg/kg orally (39). This draws attention to Ivermectin toxicity in various types of animals, the anatomical and biological features of these animals, and the method of administration.

The toxic signs that were found in our findings are consistent with the toxic signs and symptoms recorded in the rest of the animals' mice, rats, dogs, and Monkeys, which indicate the presence of symptoms specific to the central nervous system, including lethargy, stupor, ataxia, tremor, diarrhea, salivation, recumbency, and then death (36-38). High doses of ivermectin are related to neuronal depression (37) because of its action in enhancing GABA, which is the primary depressant neurotransmitter in the CNS (37).

Our results demonstrated the success of flumazenil in a dose of 0.1mg/kg i.p. to treat the signs of ivermectin poisoning, the most prominent of which are lethargy, tremors, ataxia, and salivation. Flumazenil also succeeded in preventing the death caused by ivermectin poisoning in chicks. Our results agreed with what was obtained by Al-Rakabi *et al.* (33) when studying it in mice and (37) in rats which demonstrated the ability of flumazenil to remove and suppress the acute toxic effects of flumazenil ivermectin. Ivermectin enhances GABA release and/or acts as a GABA receptor agonist, thus raising GABA-induced chloride conductivity, leading to neurons' hyperpolarization (38,39). We think it is like flumazenil GABA antagonists, which can inhibit the action of GABA and thus counteract the toxic effect of ivermectin.

Repeated doses of ivermectin at 26.3, 52.6, and 105.2 mg/kg orally cause a behavioral pattern in the open-field test represented by a decrease in locomotor activity. The tonic immobility test further suggested the depressant action of ivermectin in chicks. These effects believe the depressant action of ivermectin on the brain (40). Our results agree with the studies describing ivermectin as inhibitory effects in rodents and fish according to a measure of locomotor activity due to the inhibitory effect of ivermectin on the chloride channels (41,42).

Oral administration of ivermectin repeatedly for five days caused a significant decrease in the weight of chicks, and our study was in agreement with the previous study in pups (41). This may be due to the decrease in water and food intake caused by the depressant effects of ivermectin in chicks.

Conclusion

Ivermectin has a neurotoxic effect in chicks when used in high doses. The results indicate a potential clinical application of flumazenil for treatment side effects and toxicity of ivermectin and ivermectin, which has a depressant effect in chicks represented by open-field activity.

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Conflict of interests

There are no potential conflicts of interest, according to the authors.

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إحداث السمية الحادة للايفرمكتين في نموذج أفراخ الدجاج

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الخلاصة

يعد الإيفرمكتين عقارا آمنا للغاية، ومع ذلك، هناك العديد من الدراسات حول آثاره السامة على أنواع مختلفة من الحيوانات بسبب الحساسية أو سوء الاستخدام أو الجرعة الزائدة العرضية. كان الهدف من هذه الدراسة هو توصيف التأثيرات السمية العصبية للإيفرمكتين في الأفراخ وتحديد الاستراتيجيات العلاجية الممكنة لاستخدامها في حالات التسمم بالإيفرمكتين. تم تحديد الجرعة المميتة الوسطية للإيفرمكتين بواسطة طريقة ديكسون. تم إحداث علامات السمية الحادة للإيفرمكتين بجرعات مختلفة. تمت دراسة التأثير العلاجي للفلومازينيل على التسمم بالإيفرمكتين. تم تسجيل إعطاء جرعات متكررة من الإيفرمكتين لمدة خمسة أيام متتالية لقياس السلوك العصبي داخل صندوق الميدان المفتوح واختبار عدم الحركة الشدي. كانت الجرعة المميتة الوسطيةعن طريق الفم للإيفرمكتين ٥٢٥,٩ ملغم / كلغم. كانت علامات التسمم الحادة التي ظهرت على الأفراخ المعالجة بالإيفرمكتين هي الخمول، والرنح، والرعشة، والإسهال، والاستلقاء، ثم الموت. قلل الفلومازينيل بجرعة ٠,١ ملغم / كغم بشكل كبير من علامات السمية التي يسببها الإيفرمكتين في الأفراخ، وخاصة الرعشة والرنح، وكذلك منع حدوث الوفاة. أدى إعطاء الإيفرمكتين بجرعات ٢٦,٣ و ٥٢,٦ و ١٠٥,٢ ملغم/كغم إلى انخفاض كبير في النشاط الحركي من خلال زيادة ملحوظة في وقت بدء الحركة وانخفاض في عدد الخطوط المقطوعة. نستنتج من دراستنا الحالية إلى أن الإيفرمكتين له تأثير سام على الأعصاب في الأفراخ عند استخدامه بجرعات عالية؛ تشير النتائج أيضا إلى التطبيق السريري المحتمل للفلومازينيل لعلاج الآثار الجانبية وسمية الإيفرمكتين، وكذلك الإيفرمكتين له تأثير مثبط في الأفراخ يمثله قلة النشاط الحركي داخل الميدان المفتوح.

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