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Neurotoxicity of xylazine in chicks

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Abstract

Despite the widespread use of xylazine in veterinary medicine, studies on its neurotoxicity are limited. So, our current study aims to reveal its neurotoxicity in chicks by determining the (LD_{50}) of xylazine in Dixon's procedure. Moreover, it aims to study the effects of a small and repeated dose of xylazine on neurobehavioral test and the toxic doses of xylazine on the concentration of (glycine and glutamate) in the plasma of chicks and on the brain tissue after 60 and 90 minutes of injection. The LD_{50} of xylazine by injection into the chest muscle was 26.65 mg/kg. The injection of xylazine at a dose of 3 and 6 mg/kg in the chest muscle for three consecutive days caused an inhibition in motor activity within the open field as well as a significant elevation in the tonic immobility test response, injection of xylazine at doses 48.96 mg/kg ,60 and 90 minutes after the injection led to a significant increase in the glycine concentration as well as a significant decrease in glutamate after 90 minutes in the plasma of chicks, accompanied by histological variation in the brain tissue characterized by necrosis of neurons, vasogenic edema, neurophagia, cavities, infarction, necrosis of Purkinjean cell with decrees in the number of it. Our results revealed that xylazine had neurotoxic effects in chicks, represented by inhibition of neural behavior and motor activity within the open field, accompanied by a change in the concentration of glycine and glutamate in the plasma of chicks and histological variation in the brain tissue of chicks.

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Introduction

Xylazine is an alpha-2 adrenoceptor agonist used in veterinary practice as an analgesic, sedative, and muscle relaxant, and it is used in different animal species, including dogs, cats, horses, and sheep, cattle, rats, and deer (1-3). Xylazine reduces the release of neurotransmitters such as noradrenaline and dopamine in the central nervous system (CNS), which leads to sedation, muscle relaxation, and analgesia (4). Xylazine possesses cholinergic, serotonin, dopamine H1-histamine, or opioid receptor effects (5-8). The effects of xylazine show through a few minutes and reach to 4 hours in animals (5). Among the signs of poisoning associated with xylazine are lethargy, and high blood pressure, followed by hypotension and depression of the CNS and respiratory systems, slow heart rate, and hyperglycemia due to inhibition of insulin secretion and slow wound healing (4,5). Neurotransmitters are essential in transmitting information in the CNS as messengers in chemical synapses, the primary excitatory neurotransmitter is glutamate, and the inhibitory neurotransmitter is glycine (9). Glycine is an inhibitory neurotransmitter secreted by neurons and the brainstem in the spinal cord after synapse (10) and acts as an agonist of non-methyl-D- aspartate acid receptors, leading to depressing the CNS (9). Glutamate is one of the most important excitatory neurotransmitters in the CNS and is present in different areas of the brain, and its physiological function is to maintain brain excitability (11). Due to the lack of studies and limitations on the effects of

general anesthesia on the amino acids of neurotransmitters, especially glutamate and glycine, our study revealed some of these effects and the neurotoxicity of xylazine on the brain tissue of chicks.

Materials and methods

Experimental birds

In this study, we used broiler Rose chicks, aged 10- 14 days, that were raised in the place for breeding animals belonging to our college, under standard water conditions, feed, ventilation, and lighting.

Ethical approve

We acquired official approval for the study protocol from the Committee of Postgraduate Studies at the College of Medicine, University of Mosul, Iraq, in compliance with institutional policies on animal handling and usage research UM.VET.2022.0

Drugs

Xylazine HCl 20 mg/ml was obtained from Alfas A Company, Holland, and it was diluted in distilled water with an injection volume of 5 ml/kg of body weight. Measuring kits for glutamate and glycine were obtained from ELK Biotechnology, China.

Calculation of the intramuscular (LD_{50}) of xylazine in chicks

Six chicks were used in determining the intramuscular LD_{50} of xylazine, and their weight ranges from 125-225 g. The LD_{50} was calculated using the Dixon equation (12-14).

Effects of repeated xylazine dosages on chicks' motor activity in an open field

Eighteen chicks, weighing between 49 and 66 g, were divided into three groups at random. The first group is the control group which included 6 chicks that were injected (i.m) with normal saline for three consecutive days. The second group included 6 chicks treated with xylazine at 3mg/kg B.Wt (i.m) for three consecutive days (Representing 5% of the median lethal dose). The third group included 6 chicks that were injected with xylazine at the dose of 6 mg/kg B.Wt (i.m) for three consecutive days (It represents 10% of the median lethal dose). After 24 hours of the last treatment, the chicks in the three groups were subjected to an open field test to measure motor activity for 3 minutes (15-18) and a tonic immobility test (19).

Effect of toxic doses of xylazine on glycine and glutamate concentrations in plasma after 60 and 90 minutes

The experiment included 4 groups; 12 bird / group. First group (control group) that was treated with normal saline. The second group that was injected with xylazine at a dose of 16.32 mg/kg B.Wt. The third group was injected with xylazine at a dose of 32.64 mg/kg B.Wt. The fourth group was injected with xylazine at 48.96 mg/kg B.Wt. Blood samples were taken of each group at times 60 and 90 minutes after the injection by cutting the jugular vein for six chicks at each time. The blood samples were placed in test tubes containing the anticoagulant heparin, and the plasma was separated by centrifugation at 5000 rpm for 15 minutes. Using the ELISA kit, plasma measured amino acids (glycine and glutamate) (ELK Biotechnology, China).

Effect of toxic doses of xylazine on brain tissues after 60 and 90 minutes

From the above experiment, the brain was taken after opening the skull with forceps and scalpels, and the brain samples were placed in 10% formalin solution until tissue sections were performed within 72 hours of the injection (20,21).

Statistical analysis

In this study, the statistical program SPSS was used with a (one-way ANOVA) while the Mann-Whitney test was used to assess the non-parametric data at $P<0.05$.

Results

Calculation of the intramuscular LD_{50} of xylazine in chicks by Dixon s procedures

The acute 24-hour intramuscular LD50 of xylazine was 65,26 mg/kg B.Wt. (Table 1). The appearance of poisoning symptoms is characterized by lethargy, tease feathers, closed eyes, ataxia, and eventually death.

Table 1: The intramuscular LD_{50} of xylazine

LD_{50} of xylazine	65,26 mg/kg i.m
Range of dose of xylazine	100-60=40
Start dose	100
End dose	80
Change in dose	20a
Chicks number	6 (XXOOXO)
Onset of symptoms	1 min.

O: the animal stayed alive during 24 hours. X: the animal died during 24 hours.

Effects of repeated xylazine dosages on chicks' motor activity in an open field

Chicks treated with xylazine at doses of 3 and 6 mg/kg in the chest muscle for three consecutive days showed a significant reduction in locomotor activity represented by a significant elevation in the time of start moving, as well as a significant reduction in the number of squares, as well as a significant elevation in the length of tonic immobility correlated with the saline group (Table 2).

Table 2: The effects of xylazine dosages given repeatedly on open-field activity

Parameters	Mean ±SE (6 chicks /group)		
	Control group	3 mg/kg i.m	6 mg/kg i.m
Onset of movement (min)	1.5±0.22361	11.0±3.38625*b	3.0±0.81650*a
Lines crossed	14.5± 4.87682	3.8333±1.30171*	3.8333±1.22247*
Number of defecations	1.0± 0.25820	0.6667±0.33333	1.16667±0.40825
Jumping numbers	1.3333±0.88192	0.5000±0.22361	0.1667±0.16667
Voices of score	2.5±0.223	1.66±0.33	1.66±0.33
Pecking number	1.3333±0.55777	3.3333±0.23	5.8333± 2.40023
Tonic immobility test (second)	37.3333±8.51143	87.000±14.93988*b	137.67±110.6847*a

Values (mean ± SE) for 6 animals /group. * Significantly change from the saline group at P<0.05.

Effect of toxic doses of xylazine on glycine and glutamate concentrations in plasma after 60 and 90 minutes

The intramuscular injection of xylazine at the dose of 48.96 mg/kg after 60 and 90 minutes of injection caused a significant elevation in the concentration of glycine in plasma compared with the saline group accompanied with a significant reduction in the concentration of glutamate at the same dose after 90 minutes of injection (Figures 1 and 2).

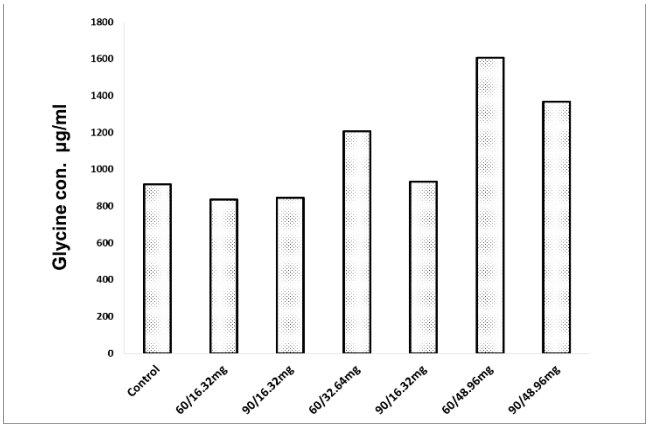

Figure 1: concentration of glycine in plasma after 60 and 90 minutes of intramuscular injected.

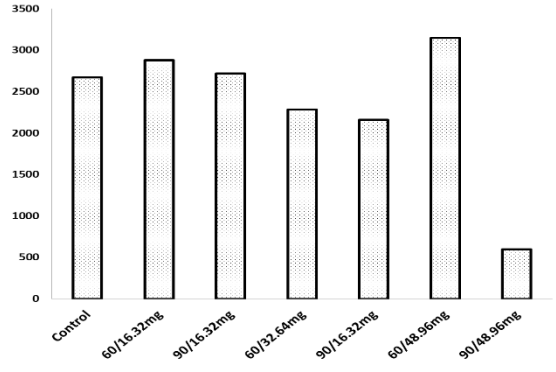

Figure 2: concentration of glutamate in plasma after 60 and 90 minutes of intramuscular injection.

Effect of toxic doses of xylazine on the brain tissues after 60 and 90 minutes

Brain section in control group showed no pathological lesions (Figure 3), while in xylazine at a dose of 16.32 mg/kg after 60minute of intramuscular injection causes neural necrosis, vasogenic edema vacuolation (Figure 4) and cerebellum discontinuation (Figure 5), while xylazine at a dose of 32.64 mg/kg body weight after 60 minutes of treatment showing necrosis of pyramidal cells (Figure 6). infiltration of inflammatory cells (Figure 7), neurophagia (Figure 8), vasogenic edema and vacuolation of neurons (Figure 9), cavities and pyramidal cell necrosis (Figure 10). At the same time, xylazine at the same dose after 90 minutes causes infraction (Figure 11), with necrosis of granular cells, necrosis of Purkinjean cells in the brain of chicks treated with xylazine at a dose of 48.96 mg/kg after 60 minutes of intramuscular injection (Figure 12), congested blood vessels (Figure 13). Xylazine at a dose of 48.96 mg/kg body weight after 90 minutes of treatment showing necrosis, necrosis of granular cells layer, congested blood vessel (Figure 14), and necrosis of Purkinje cells (Figure 15), and necrosis of granular cell layer (Figure 16).

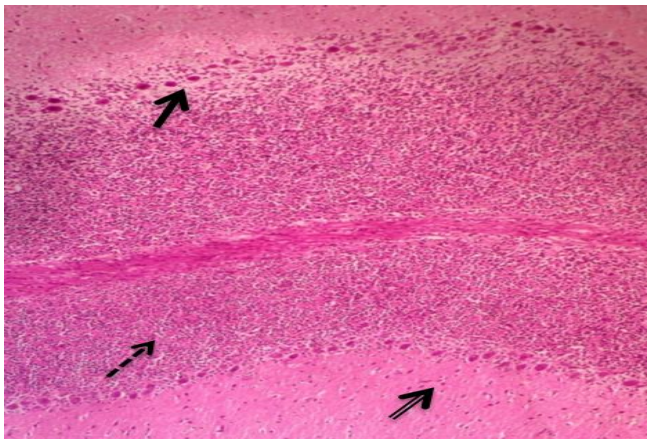

Figure 3: Cerebellum of chicks (Control) showing the normal structure of cerebella layers (arrow), granular cell layer (segmented arrow) molecular layer (parallel arrow). H&E, 10x.

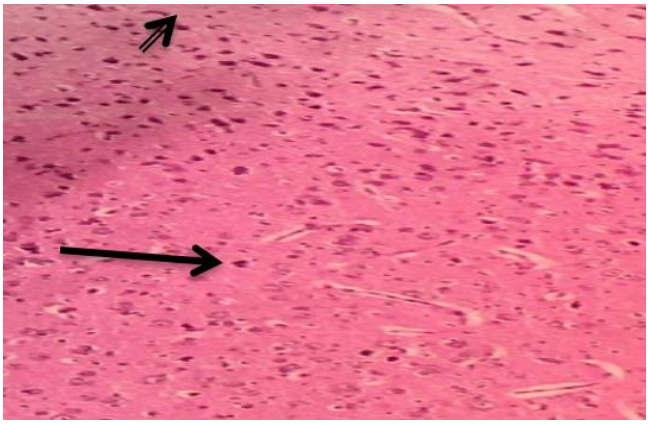

Figure 4: Brain of chicks treated with xylazine at dose 16.32mg/kg body weight after 60 minute of treatment showing neural necrosis (arrow), vasogenic edema and vacuolation (parallel arrow). H&E, 10x.

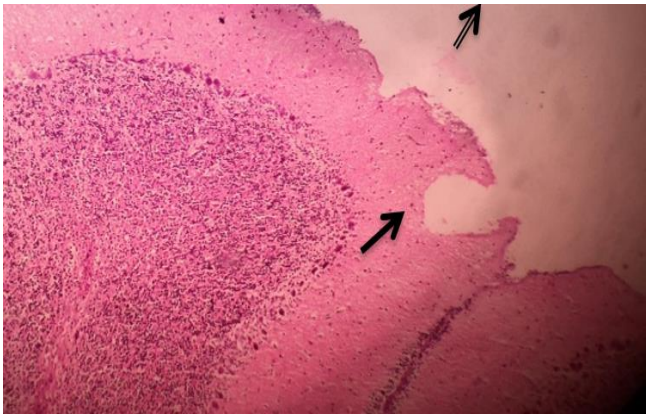

Figure 5: Cerebellum of chicks treated with xylazine at dose 16.32mg/kg body weight after 90 minute of treatment showing cerebellum discontinuation (arrow). H&E, 10x.

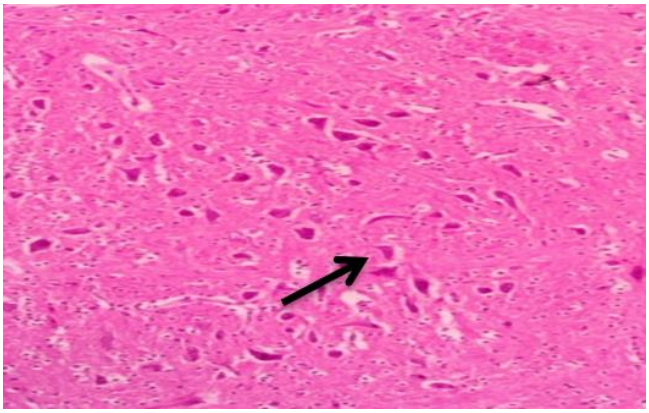

Figure 6: Cerebrum of chicks treated with xylazine at dose 32.64mg/kg body weight after 60 minute of treatment showing necrosis of pyramidal cells (arrow). H&E, 10x.

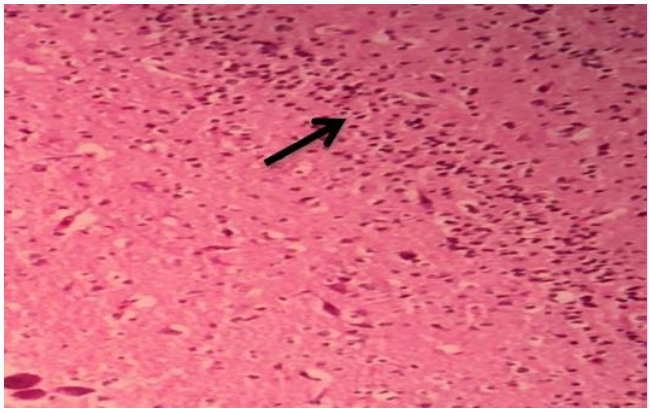

Figure 7: Brain of chicks treated with xylazine at dose 32.64mg/kg body weight after 60 minute of treatment showing infiltration of inflammatory cells (arrow). H&E, 10x.

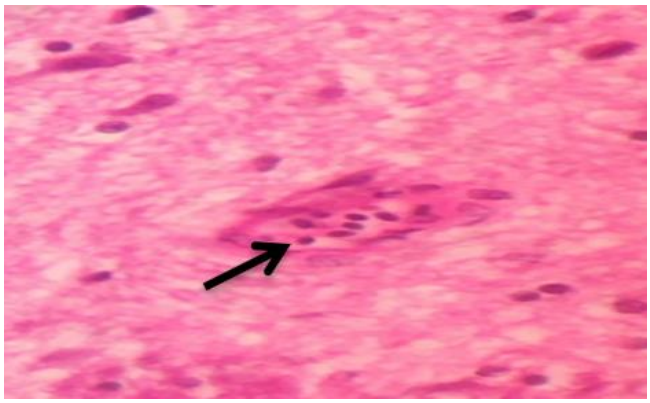

Figure 8: Brain of chicks treated with xylazine at dose 32.64 mg/kg body weight after 60 minutes of treatment showing neurophagia (arrow). H&E, 10x.

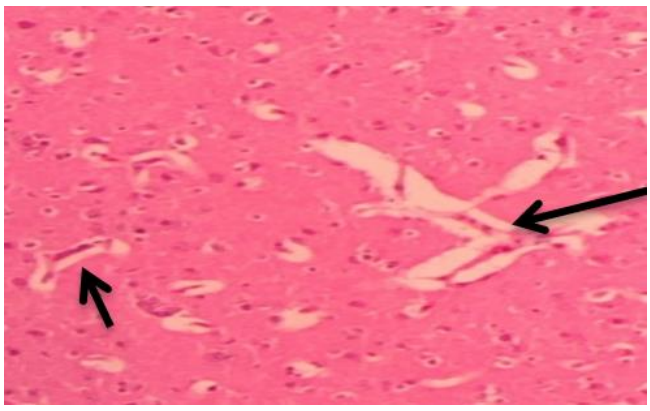

Figure 9: Brain of chicks treated with xylazine at dose 32.64mg/kg body weight after 60 minute of treatment showing vasogenic edema and vacuolation of neurons (arrow). H&E, 10x.

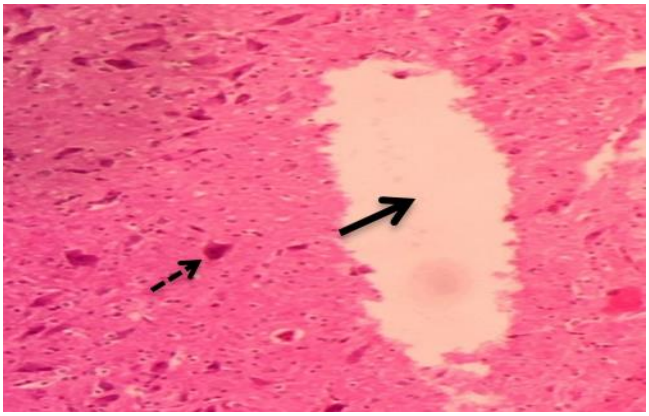

Figure 10: Brain of chicks treated with xylazine at dose 32.64 mg/kg body weight after 60 minute of treatment showing cavities (arrow) pyramidal cell necrosis (parallel arrow). H&E, 10x.

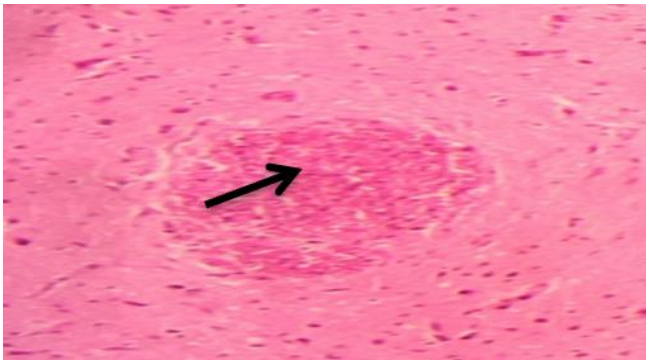

Figure 11: Brain of chicks treated with xylazine at dose 32.64 mg/kg body weight after 90 minute of treatment showing infarction (arrow). H&E, 10x.

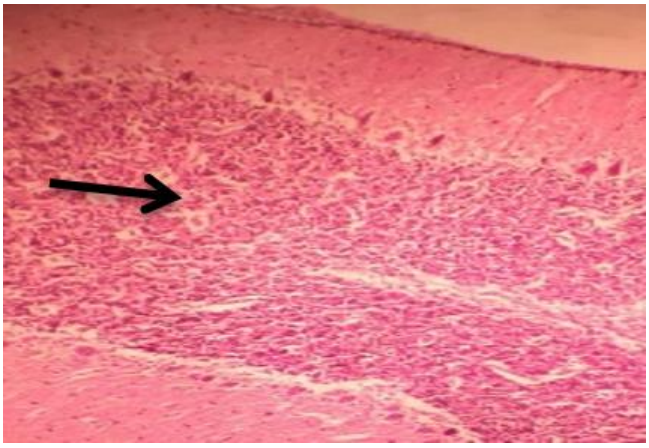

Figure 12: Brain of chicks treated with xylazine at dose 48.96mg/kg body weight after 60 minute of treatment showing necrosis of granular cell and necrosis of Purkinjean cells (arrow). H&E, 10x.

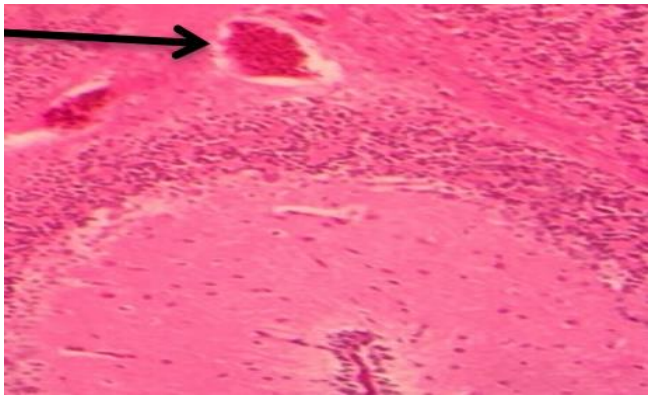

Figure 13: Brain of chicks treated with xylazine at dose 48.96mg/kg body weight after 60 minute of treatment showing congested blood vessel (arrow). H&E, 10x.

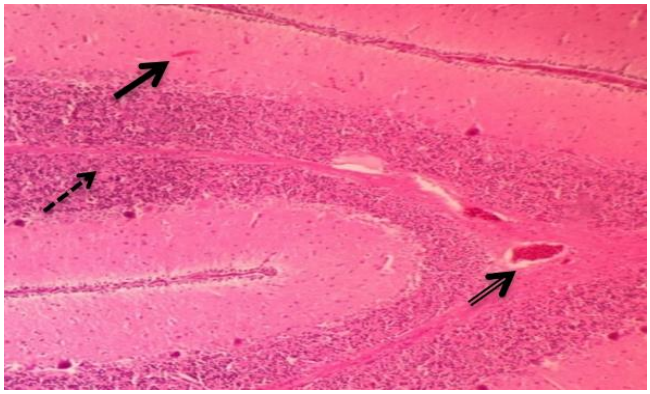

Figure 14: Brain of chicks treated with xylazine at dose 48.96mg/kg body weight after 90 minute of treatment showing necrosis (arrow) necrosis of granular cells layer (segmented arrow), congested blood vessel (parallel arrow). H&E, 10x.

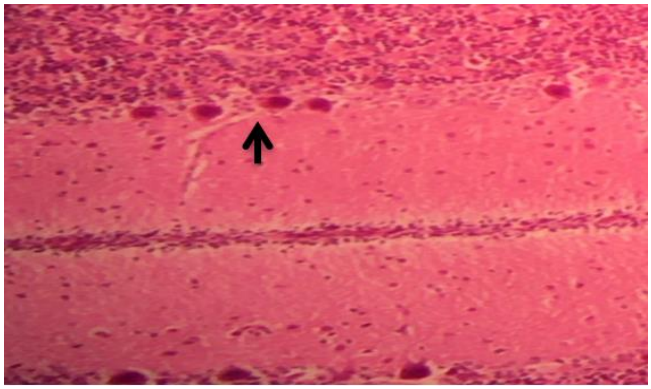

Figure 15: Brain of chicks treated with xylazine at dose 48.96mg/kg body weight after 90 minute of treatment showing necrosis of Purkinjean cell with depletion in the number of it (arrow). H&E, 10x.

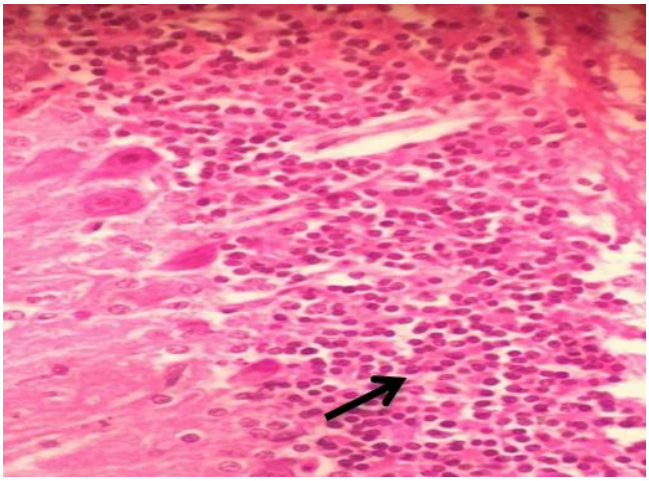

Figure 16: Brain of chicks treated with xylazine at dose 48.96mg/kg body weight after 90 minute of treatment showing necrosis granular cell layer (arrow). H&E, 10x.

Discussion

Xylazine is known as a central and peripheral nervous system depressant. This inhibition occurs by stimulating α-2-adrenergic receptors located in the pre-synaptic ends of neurons, which leads to a decrease in calcium entry and thus reduces the secretion of noradrenaline in the central and peripheral nervous system (22,23). Our study sought to determine the neurotoxicity of xylazine in a chick's model by determining the LD50 by intramuscular injection. The dose was 65.26 mg/kg,

while the LD50 in rodents, dogs, and cats differed according to the method of administration, as it was 22-43mg/kg intravenously, 47mg/kg when intramuscularly, and 130-240 mg /kg orally, while in horses it was 60-70 mg by intramuscular injection, the most important signs of poisoning that appeared on animals' lethargy, convulsion, salivation and vomiting (24,25). The difference in the median lethal dose may be due to the difference in the type of animal and the method of administration.

One of the common tests in measuring the activity and behavior of laboratory animals such as rodents and chicks is the open field test (26), which was used in this study to detect the latent effects with small and repeated doses of xylazine. In this study, it was observed that xylazine inhibits the nervous behavior and motor activity within the open field of chicks by increasing the moment when the movement began and the reduction in the number of squares crossed, as well as an increase in the response time to tonic immobility test. Our results agreed with the researchers (27) in chicks and mice (28). For the first time in our study, the concentration of glycine and glutamate in plasma was measured after 60 and 90 minutes of xylazine injection. In our study, conducted during anesthesia with xylazine, we noticed an increase in glycine concentration in the plasma and a decrease in the concentration of glutamate after 90 minutes of injection, and the concentrations changed irregularly (29).

The high glycine concentrations in the plasma may be due to the role of xylazine in promoting the synthesis and release of glycine, which reduces the excitability of neurons and thus leads to anesthesia (29). The decrease in the concentration of glutamate is due to the effect of xylazine in inhibiting the synthesis of glutamate, which reduces the excitatory neurotransmitter and ultimately reduces the stimulation of neurons and the production of an anesthetic effect (30). Past results have confirmed that doses of barbiturates inhibit the secretion of aspartate and thus depress the (CNS), leading to a narcotic effect (31,32). This is what was shown by the past results that isoflurane works to inhibit aspartate and enhances the role of glycine in the (hippocampus and spinal cord), and this inhibits the transmission of excitatory amino acids in the synapses, leading to depressing the (CNS), which produces an anesthetic effect (33,34). In agreement with past results, we expected that the anesthetic effect of xylazine might be due to the suppression of the excitatory neurotransmitters and enhancement of the release of inhibitory neurotransmitters. In addition, GABA and glycine receptors are similar in their function in that they both raise the concentration of Cl-in neurons, leading to hyperpolarization and general anesthesia (35-37). The study of histopathological changes is one of the most important biomarkers of animal exposure to pathogenic factors, whether physical or chemical, which leads to tissue and cellular damage. Our study noted that the treatment of chicks with xylazine at times of 60 and 90 minutes led to pathological tissue changes in the brain, including necrosis of Purkinje cells, granular cells, and pyramidal cells. These changes were similar or consistent with what the researchers said in a study conducted on monkeys, where anesthesia with xylazine and ketamine caused brain cell necrosis (38). Anesthetizing monkeys with xylazine and ketamine leads to acute neurological damage in the brain and spinal cord caused by several factors, including the hypotension caused by xylazine (39). In baboons, arterial hypertension, followed by subsequent hypotension, leads to brain neuron damage (40). Low arterial blood pressure causes brain and spinal cord ischemia, leading to necrosis of the border areas between the arterial regions (41).

Conclusion

Our results revealed that xylazine had different effects on the neurotransmitters of amino acids by increasing the concentration of glycine and decreasing the concentration of glutamate, especially after 90 minutes of injection, which may be one of the main mechanisms of anesthesia with xylazine. In addition, xylazine had acute neurotoxicity effects represented by histological changes in the brain.

Conflict of interest

The researchers don't have any competing interests.

Acknowledgments

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السمية العصبية للزيلازين في أفراخ الدجاج

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الخلاصة

على الرغم من الاستخدام الواسع النطاق للزيلازين في الطب البيطري، فإن الدراسات حول سميته العصبية محدودة. لذلك ارتأت دراستنا الحالية الكشف عن سميته العصبية في الأفراخ كنموذج للدراسة، من خلال تحديد الجرعة المميتة الوسطية باستخدام طريقة الصعود والنزول في الجرعة وبحسب ديكسون، ودراسة تأثير الجرع القليلة والمتكررة من الزيلازين على النشاط الحركي في صندوق الميدان المفتوح وكذلك دراسة الجرعات السامة من الزيلازين على تركيز الكلايسينوالكلوتاميت في بلازما دم الأفراخ واخذ مقاطع نسيجية للدماغ بعد ٦٠ و ٩٠ دقيقة من الحقن. كان متوسط الجرعة المميتة للزيلازين عن طريق الحقن في عضلة الصدر ٢٦,٦٥ ملغم/كغم. تسبب حقن الزيلازين بجرعة ٣ و ٦ ملغم/كغم في عضلة الصدر لمدة ثلاثة أيام متتالية في تثبيط النشاط الحركي داخل الميدان المفتوح بالإضافة إلى زيادة ملحوظة في وقت استجابة لاختبار عدم الحركة الشديد، سببالزيلازين بالجرع ٤٨,٩٦ ملغم/كغم في عضلة الصدر بعد ٦٠ و ٩٠ دقيقة من الحقن إلى زيادة معنوية في تركيز الكلايسين وكذلك انخفاض معنوي في الكلوتاميت بعد ٩٠ دقيقة في بلازما دم الأفراخ، مصحوبة بتغيرات نسيجية في دماغ الأفراخ المتمثلة بنخر الخلايا العصبية، وذمة وعائية المنشأ، والتهاب الأعصاب، والتجاويف، والاحتشاء، تنخر في خلايا بركنجي مع انخفاض عددها. أظهرت نتائجنا أن الزيلازين له تأثيرات سامة عصبية في الأفراخ تتمثل في تثبيط السلوك العصبي والنشاط الحركي داخل الميدان المفتوح، مصحوبًا بتغير في تركيز الكلايسينوالكلوتاميت في بلازما دم الأفراخ وتغيرات نسيجية في دماغ الأفراخ.