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Evaluation of the Anesthetic Action of Alfaxalone in Chicks and Compared with Alfaxalone/ketamine or Alfaxalone/xylazine.

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OBJECTIVE, alfaxalone is a neuro-steroidal anesthetic agent. The data on the anesthetic properties of alfaxalone in the birds is relatively inadequate. This article studies the anesthetic effect and efficiency of alfaxalone /ketamine or alfaxalone /xylazine anesthesia given in 7-10 day-old chicks. Methods, We used the up and down method to determine the median effective anesthetic dose of alfaxalone, time to onset of anesthesia, duration of action, temperature, respiratory rate, and antagonize with flumazenil were evaluated. Results, The median effective anesthetic dose (ED_{50}) of alfaxalone was 32.88mg/kg . intraperitoneally. Alfaxalone at 25, 50, and 100 mg/kg induced anesthesia in chicks for (10 - 48 minutes). Flumazenil decreased the anesthetic period of alfaxalone. Alfaxalone at 50mg/kg causes bradypnea whereas at 100 mg/kg causes tachypnea. Alfaxalone produce hypothermia. The duration of anesthesia was significantly longer in alfaxalone/xylazine than in alfaxalone/ketamine but it causes more bradypnea. Conclusion, alfaxalone produces light surgical anesthesia so that it can be mixed with ketamine or xylazine for deep surgical anesthesia. Flumazenil may reverse the anesthetic effect of alfaxalone.

Keywords: Chicks, Alfaxalone, Anesthesia, Ketamine, Xylazine, Flumazenil.

Introduction

Alfaxalone (3a-hydroxy - 5a- pregnane- 11, 20-dione) is a steroidal-anesthetic agent which activates allosteric binding site of the A gamma-aminobutyric acid type A (GABAA) receptor[1]. The early form of alfaxalone, first introduced in 1971, was insoluble in water, and polyoxyl castor oil was used to improve solubility. This subsequent product, however, caused hypersensitivity symptoms [2] and was pulled from the market. The other most recent commercial production of alfaxalone compounds with 2-hydroxypropyl-β-cyclodextrin allows its solubility in an aqueous solution. The medication is labeled for intravenous injection in dogs and cats. Additional data on the use of alfaxalone in pigs[3], horses[4] and rats[5] have been collected, but the data for chicks are restricted. Alfaxalone has been used in birds during the last 40 years as a general anesthetic [6,7,8]. alfaxalone was utilized in the induction and maintenance of anesthesia in bird species [9]. However, dogs, cats[10], humans[11], and birds[6], sometimes had allergic reactions[11,12] to the diluent Cremophor-EL. The existing product (Alfaxan, Jurox (UK) Ltd., Crawley, West Sussex RH10 1DD, UK) uses 2-hydroxypropyl-b cyclodextrin as a solubilizing material and has not been related to releasing of histamine [13,14].

The allosteric modulation will potentiate the GABA effect on the receptor which is a ligand-gated chloride ion (Cl^-) channel is the primary mechanism of alfaxalone anesthetic action, which prevents neuronal excitability[15]. Alfaxalone binds directly to GABAA receptors, enhances endogenous GABA effects, contribute to increasing chloride ions influx, neuronal hyperpolarization, and inhibiting the possible action potential [16]. The GABAA receptor is a pentameric transmembrane ion channel at which

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pharmacological possessions of interrelating remedies are determined by both the receptor subunit structure and by remedy subunit choosiness. In the CNS many different GABA A receptor isoforms are present and they differ in receptor's agonist affinity, the chance of opening, conductance, and other properties [16,17] .

The sub-anesthetic IM dose of alfaxalone might yield sedative action, the effect is similarly leading to hyperpolarization of the cell, just a slightly different mechanism. Due to its water insolubility, originally alfaxalone ingredients, (e.g. Saffan®) were solubilized and formulated by an alfadolone with 20 % of Cremophor EL. Due to a complication caused by an increased histamine release by liquid solubilization, such as ear pinnae and forepaw hyperemia among cats, and recurrent pits in adults and herbicides, however, this product was voluntarily discontinued from the market [18] and dogs suffer from anaphylactic reaction due to histamine release [19] .

The aim of this study was to evaluate the efficacy and safety of intraperitoneal alfaxalone for general anesthesia in chicks and compared its anesthetic effect with the xylazine and ketamine.

Materials and Methods

Animals

One day old Ross broiler chicks of both males and females were purchased from a local regional hatchery and housed until the age of 7-10 days once the experiments were carried out. All birds were placed in a room with a heat of 33-35 ºC, 23-hour light, and one hour dark and wooden shavings as floor litter, with free access to water supplies and poultry nutrition.

Drugs and chemicals

Sterile distilled water was used to dilute each drug to an appropriate concentration at the time of use .The alfaxalone (10mg/ml, ALFAXAN, Jurox Pty. Ltd., Rutherford, NSW, Australia) was injected intraperitoneally (i.p.) in a volume of 5 ml/kg body weight[20] . Xylazine (2%, Xyla, Holland), Ketamine (10 % injectable solution, DOPHARMA Netherland), Flumazenil (0.5 mg/ml, Mylan, SAS, France) were injected intramuscularly (IM) route (5 ml/ kg, IM). The studies have been carried out in compliance with the institutional guidelines of animal care, welfare and humane care, which are based on the recommendations of the National Research Council [21] .

Evaluation of alfaxalone median effective dose (ED_{50}) for anesthesia

It corresponds to a degree of the influence of a drug, being the dose of a drug necessary to yield 50% of that drug's maximal effect of alfaxalone for the anesthetic induction in young chicks. The initiation of anesthesia was described as a lack of righting reflex until the chicks were softly put on one face [22, 23]. In the beginning, the dose that leads to anesthesia was fixed and one chick was injected with this dose intraperitoneally, after which the result was determined, which is analgesia or not and the rate of increase or decrease in the dose of alfaxalone was Subsequent to a fixed amount of 0.2 mg / kg b.w and by repeating this method by ascending and descending the dose to a number of chicks (we evaluate 3 chicks after change in pharmacological effect from anesthetic to non-anesthetic effect or vice versa) , enabling us to calculate the median effective dose (ED_{50}) of alfaxalone based on the table mentioned[24] and Using the following equation,

$ED_{50} = Xf + Kd$

Whereas

Xf = the last dose used in the experiment.

K = a tabular value extracted from the table mentioned by Dixon[24] .

d = ± in the administered dose

Evaluation of multiple doses of alfaxalone for anesthetic effect

In this experiment we used 24 chicks that distributed equally into three groups. Group 1,2 and 3 were injected with alfaxalone at 25, 50, and 100 mg/kg IP respectively then the onset and duration of the loss of the righting reflex were calculated for the all chicks .we calculated the anesthetic duration from the time of loss of righting reflex until the time of recovery and standing without any aids.

Antagonistic effect of flumazenil against alfaxalone induced anesthesia

A total of 32 chicks were randomly distributed into 4groups of 8 chicks each. All groups were treated by alfaxalone at 50 mg/kg. Then all groups injected with flumazenil at 0 (control), 0.05, 0.1 and 0.2 mg/kg IM directly after the alfaxalone injection the chicks. we chose the doses of flumazenil from the previous literatures [25, 26]. The duration of anesthesia was calculated according to the previous experiment for all groups then we determined the percentage of decrease in duration of anesthesia.

The anesthetic effect of alfaxalone on temperature and respiratory rate

In this experiment we used 24 chicks that distributed equally into three groups. Group 1, 2 and 3 were injected with alfaxalone at 25, 50, and 100 mg/kg IP respectively .Then, body temperature and respiratory rate were measured before and after loss of righting reflex. Body temperature was measured by placing a Digital Laser Infrared Thermometer Temperature Gun (China Supplier - Diamond Member Audited Suppliers SHENZHEN CHEERMAN TECHNOLOGY CO., LTD) on the chest area.

Comparison of anesthetic effect of alfaxalone, alfaxalone /ketamine and alfaxalone/ xylazine

In this experiment we used 24 chicks that distributed equally into three groups. Group 1 administrated alfaxalone at 50mg/kg, IP , group 2 administered alfaxalone at 50mg/kg IP and ketamine at 20mg/kg IM and group 3 administrated alfaxalone at 50mg/kg IP and xylazine 5mg/kg IM . Then we measure the onset of action, duration of anesthesia, and respiratory rate at the loss of the righting reflex for each group. We chosed the doses of xylazine and ketamine according to the prevoius studies[22].

Statistical Analysis

Statistical analyses were achieved using SPSS program version 16.0, The data was represented as mean + standard error. Statistical analysis was performed using one-and two-way variance analysis followed by an LSD test. $P<0.05$was considered significant [27] Pre-Post Data was analyzed by paired sample t -test.

Results

Evaluation of alfaxalone median anesthetic dose (ED_{50}).

The ED_{50} of alfaxalone for the initiation of anesthesia in the chicks was 32.88 mg/kg, IP (Table 1).

Evaluation of multiple doses of alfaxalone for anesthetic effect

Alfaxalone at 25, 50 and 100 mg/kg intraperitoneally meaningfully and in a dose-dependent manner diminished the onset of anesthesia in the chicks and increase anesthetic duration (Table 2). Alfaxalone at 25 mg/kg produced lateral recumbancy in chicks (12%), while Alfaxalone at 50 and 100 mg / kg IP produced LORR and lateral recombancy in chicks by 100%, (Table 2). Alfaxalone at 25 mg /kg IP provoked recumbence on sternum and shut eyes chicks, while the other groups provoked a LORR. (Table 2).

TABLE 1. Median effective dose of alfaxalone for initiation of anesthesia in chicks

Variables	Results
ED_{50}	32.88mg/kg ip
The dosage range use	50-20=30 mg/kg
Primary dose	40 mg/kg
Final dose	20 mg/kg
± in the dose	10 mg/kg
Chicks used	(OXXXO) 5
Onset of action (lowest-highest)	2-6 minute
(Duration (lowest-highest	4-6 minute

X, anesthesia (LORR) , O, no anesthesia, The median anesthetic dose ED_{50} was calculated through the up-and-down manner

TABLE 2. Evaluation of multiple doses of alfaxalone for anesthetic effect

Alfaxalone	(Onset of anesthesia (min	(Duration of anesthesia (min	LORR %
25	4.21±0.49	9.91±0.53	12.5
50	□1.87±0.24	□37.88±5.32	100
100	□1.13±0.06	a□48.25±2.55	100

Values represent mean ± standard error of 8chicks for each group
□ Significantly dissimilar with the alfaxalone at 25mg/kg, $p < 0.05$
a Significantly dissimilar with the alfaxalone 50mg/kg $p < 0.05$

Antagonistic effect of flumazenil against alfaxalone50mg/kgIP induced anesthesia

Flumazenil at 0.05, 0.1 and 0.2 mg/kg IM reduced the anesthetic period of chicks treated with alfaxalone at 50 mg/kg, intraperitoneally in a dose-dependent manner (Table 3).

The anesthetic effect of alfaxalone on temperature and respiratory rates.

Alfaxalone at 25, 50 and 100 mg/kg significantly reduce the body temperature and cause tachypnea in dose dependent manner before loss of righting reflex. Alfaxalone at 25 and 50mg/kg cause tachypnea after loss of righting reflex whereas alfaxalone at 50mg/kg cause bradypnea (Table 4).

Comparison of anesthetic effect of alfaxalone, alfaxalone /ketamine and alfaxalone/xylazine

The duration of anesthetic action for alfaxalone/ketamine was higher than for alfaxalone alone and the duration of anesthetic action for alfaxalone/xylazine was higher than for alfaxalone/ketamine and alfaxalone alone respectively. The onset of action of alfaxalone/ketamine and alfaxalone/xylazine was shorter than alfaxalone alone. The administration of alfaxalone/ketamine and alfaxalone/xylazine significantly reduce the respiratory rate in comparison to alfaxalone alone (Table 5).

TABLE 3. Antagonistic effect of flumazenil against alfaxalone induced anesthesia .

Alfaxalone	Flumazenil mg/kg IM	Duration of anesthesia in minute	decrease in duration of sleep time %
50mg/kg IP	0(saline)	36.91 ± 2.27	0
50mg/kg IP	0.05	30.10 ± *3.10	18
50mg/kg IP	0.1	28.53 ±3.06 *	22
50mg/kg IP	0.2	21.75±2.29 a*	41

Values represent mean ± standard error of 8 chicks for each group. Flumazenil was given intramuscularly directly next the intraperitoneal injection of alfaxalone at 50 mg/kg.
* Significantly dissimilar with the parameter of group1, $p < 0.05$.
a, Significantly dissimilar with the parameter of groups 2, respectively, $p < 0.05$

TABLE 4. The anesthetic effect of alfaxalone on temperature and respiratory rates

Alfaxalone	Before LORR		After LORR	
	Temperature	Respiratory rate	Temperature	Respiratory rate in one min
25	36.45±0.13	43.50±0.57	35.25±0.02#	50.75±1.37 δ
50	35.55±0.08	50.25±1.37	35.31±0.09#	43.00±3.53 δ
100	35.57±0.05	53.75±0.81a	35.27±0.10#	64.00±5.31 δ

Parameters represent mean ± standard error of 8 birds for every group
Significantly dissimilar with alfaxalone at 25mg/kg, $p < 0.05$
a Significantly dissimilar with alfaxalone at 50mg/kg, $p < 0.05$
#Significantly dissimilar with parameter of before LORR for body temperature , $p < 0.05$
δ Significantly dissimilar with parameter of before LORR for respiratory rate , $p < 0.05$

TABLE 5. Time to onset, duration of action and respiratory rate of alfaxalone alone or in combination with ketamine or xylazine.

Groups	Onset of anesthesia	Duration of anesthesia	Respiratory rate at LORR
alfaxalone	3.29±0.54	36.91±2.72	42.25±2.42
Alfaxalone /ketamine	1.24±0.07	61.85±21.89	35.50±0.88
Alfaxalone /xylazine	1.24±0.06	117.93±41.69	21.50±2.42a

Parameters represent mean ± standard error of 8 chicks for each group
Significantly dissimilar the alfaxalone, $p < 0.05$
a Significantly dissimilar from the parameters of groups administered with Alfaxalone /ketamine , $p < 0.05$

Discussion

Anesthesia is an important and vital process of bird medicine and surgery. Bird has special structural and physiological traits that have a powerful role on anesthesia. Awareness and understanding of the features of the cardiovascular and respiratory systems of birds are essential for the proper choice and administration of anesthetics[28, 29]. In this study, we demonstrate the median anesthetic dose of alfaxalone using up and dawn method which was 32.88 mg/kg intraperitoneally , the anesthetic dose in some other birds species like mute swan 10mg/kg intravenously[30] and rose flamingos 2mg/kg intravenously for induction of anesthesia [31] And the differences of doses may be due to the route of administration. However, The Material Safety Data Sheets for alfaxalone indicate that the LD_{50} in rats is 19 mg/kg IV, while the LD_{50} was116 mg/kg intraperitoneally. Modification of solubility can cause difference in the bioavailability or pharmacokinetics of alfaxalone in various matrices, such as the abdominal cavity. In plasma, 2-hydroxypropyl-β-cyclodextrin is directly degraded by hydrolysis and catalytic enzymes[32]. Alfaxalone at 50 and 100 mg/kg caused a light surgical plane of anesthesia for 38 and 48 min respectively, with a 2-1 min onset. Flumazenil competitively prevents benzodiazepine-recognition action at the GABA / benzodiazepine receptor complex, thus preventing the actions of benzodiazepines and other drugs like alfaxalone[33]. Flumazenil was tried to be used in the our article to overcome the anesthetic effect of alfaxalone in chicks, as it was described to opposite some anesthetic agent in dogs[33]. Flumazenil at 0.05, 0.1 and 0.2 mg/kg IM successfully diminish a period of alfaxalone anesthesia in the chick's by18, 22 and 41%, respectively. Flumazenil also reverse the anesthetic effect of alfaxalone and midazolam in Egyptian fruit bats[34]. The possible mechanism of the flumazenil by which reduce the duration of general anesthesia is the inverse agonist activity of the GABAA receptor in the central nervous system[26, 33, 35, 36]. Body temperature and respiratory rates were initially found to be significantly different between groups (25, 50 and 100mg/kg) and after loss of righting reflex. After initiation of general anesthesia, the drop in body heat happens in 3 steps. The highest drop happens through the first 15min or step 1. Usually, body temperature is kept in an unequally spread way, the heat of core tissues is 2 ^{0}C to 4 ^{0}C larger than cutaneous heat. After anesthesia initiation, however, blood vessels undergo vasodilation followed by a dropped cold threshold in the hypothalamus lets redistribution of body temperature from core tissues to the skin, where the temperature is declining mainly through radiation. Step 2 begins followed about 1hour, as core heat drops at a slower rate and proceeds in a linear way as temperature drop from the body exceeds heat production. Lastly, After 3 to 5 hours, step 3 starts, when an equilibrium is achieved where the temperature drop is coordinated by the output of heat and thermo-regulated vascular constriction begins to function[37, 37, 38] . Alfaxalone at 50mg/kg cause a decrease in respiratory rate whereas at 100mg/kg cause increase in respiratory rate however, Alfaxalone makes a dose-dependent reduction in breathing rate and minute volume like to propofol[39] Numerous articles have not detected post-induction apnea after recommended clinical relevant doses of alfaxalone were administered intravenously over about 60 second [39] however , one research did not detect any post induction apnea in cats treated with over clinical dose (25 mg/kg intravenously above 60 second) of alfaxalone [40] . Alfaxalone caused a significantly lower body temperature after the LORR time point compared to a time before the LORR, but the variation of body temperature is indeed not likely to be clinically relevant. The central pharmacological activity of alfaxalone, ketamine, and xylazine varies considerably to the receptors and neurotransmitter systems concerned. Several studies explored the combined effects of alfaxalone-xylazine in rats[41] or alfaxalone-ketamine in rats [42] To minimize side effects and lower doses for improved anesthetic activity of medications. Alfaxalone could be co-administered with numerous anesthetics agent to yield effective balanced anesthesia .The combination of alfaxalone / xylazine produce a longer duration of anesthesia compared with alfaxalone alone and alfaxalone /ketamine but it produces a higher incidence of bradypnea in compared with alfaxalone alone and alfaxalone /ketamine groups, our finding is similar to the previous studies on the mice[41, 42] , rats[43] , horses[44] , calves [45].

In conclusion, alfaxalone produces light surgical anesthesia so that it can be mixed with ketamine or xylazine for deep surgical anesthesia. Flumazenil may reverse the anesthetic effect of alfaxalone these results are it could be

scientifically useful in the avian species, or it could be enhanced to mammals following further trials.

Authors' Contributions

Both authors worked equally and approved the final manuscript.

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Conflict of interest

The researchers claim that they do not have competing interests.

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تقييم الفعل المخدر للالفاكسالون في افراخ الدجاج و مقارنته مع مزيج الالفاكسالون/ الكيتامين او مزيج الالفاكسالون / الزيلازين

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الالفاكسالون مخدر عصبي ستيرويدي و لقلة البيانات المتعلقة بالالفاكسالون عند استعماله كمخدر في الطيور تم اجراء هذا البحث . ان الهدف من هذه الدراسة في دراسة التاثيرالمخدر وكفاءة استخدام مزيج ألفاكسالون / كيتامين أو مزيج ألفاكسالون / زيلازين في افراخ الدجاج التي يتراوح عمرها ما بين ٧-١٠ أيام حيث تم تقييم الوقت المستغرق لبدء التخدير ومدة التخدير ودرجة الحرارة ومعدل التنفس و التضاد مع الفلومازينيل. و كانت الجرعة المخدرة الوسطية للالفاكسالون عند اعطائه عن طريق الخلب هي ٣٢,٨٨ ملغم/كغم من وزن الجسم . ادى حقن الافراخ بالالفاكسالون عن طريق الخلب بجرع ٢٥ و ٥٠ و ١٠٠ ملغم/كغم من وزن الجسم الى زيادة في وقت التخدير بشكل معتمد على الجرعة و كانت مدة التخدير ما بين ١٠ الى ٤٨ دقيقة و كان للفلومازينيل تأثيرا ضادا للفعل المخدر للالفاكسالون . و ادى حقن الالفاكسالون بجرع ٥٠ملغم/كغم الى تباطئ في ترداد التنفس في حين ادت الجرعة ١٠٠ملغم/كغم الى تسارع في ترداد التنفس و كان للالفاكسالون تاثيرا خافضا لدرجة الحرارة بالجرع المخدرة و كانت مدة التخدير اطول عند استخدام مزيج الالفاكسالون مع الزايلازين بالمقارنة مع مزيج الالفاكسالون و الكيتامين و نستنج من دراستنا ان للالفاكسالون تأثيرا مخدرا خفيفا و من الممكن حقنه مع الزايلاين او الكيتامين لينتج تخديرا جراحيا عميقا و بامكان الفلومازينيل من التقليل من التاثير المخدر للالفاكسالون

الكلمات المفتاحية: افراخ الدجاج ، الالفاكسالون ، التأثير المخدر ، الكيتامين ، الزيلازين.