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Y. MOUSA

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Etomidate anesthesia in chicks: Effect of xylazine

Y. Mousa

Department of Physiology, Biochemistry and Pharmacology, College of Veterinary Medicine, University of Mosul, Mosul, Iraq

ABSTRACT: The current study aimed to evaluate the etomidate anesthetic action, its toxicity profile and safety alone and to determine the benefit of xylazine coadministration to enhance its anesthetic duration, efficacy and to reach a state of balanced anesthesia in chicks. By using the up-and-down technique, it was found that the hypnotic Median Effective Dose (ED_{50}) of the etomidate was 4.30 mg/kg, IM, whereas the acute Median Toxic Dose (TD_{50}) was 17.90 mg/kg, IM in the chicks. In response, the calculated Therapeutic Index (TI) and Standard Safety Margin (SSM) indicate that the etomidate has a wide safety margin. Etomidate injection at 4, 8 and 16 mg/kg, IM yields a significant dose-response and dependent hypnosis in the chicks by evaluating the onset of the righting reflex loss, its period and regaining from it. The combination composed of etomidate and xylazine at 5 mg/kg, IM for each, reduced the onset of hypnosis and significantly distended its period besides a significant rise of the recovery time when compared with the group receiving etomidate alone. At the same time, this coadministered drugs elicited a significant raise in analgesic efficacy. Concerning plasma glucose, Alanine Transaminase (ALT) and Aspartate Transaminase (AST) concentrations, neither etomidate nor etomidate plus xylazine differ significantly from the control group. The results of this study propose the likelihood of using etomidate as an anesthetic agent for short surgical trials in the chickens that can be more effective by using xylazine to yield balanced anesthesia without causing significant side effects.

Keywords: Analgesia, chicks, etomidate, hypnosis, xylazine

Corresponding Author:

Yaareb J. Mousa, Department of Physiology, Biochemistry and Pharmacology, College of Veterinary Medicine, University of Mosul, Mosul-Iraq
E-mail address: yarub204@uomosul.edu.iq

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INTRODUCTION

Etomidate is an imidazole derivative that belongs to non-barbiturate anesthetics acting as a short anesthetic agent used for rapid induction of general anesthesia. The mechanism by which etomidate induced anesthesia via its potentiation of the neurotransmitter Gamma Aminobutyric Acid (GABA) and tighten its binding to GABA_A receptor, leading to depression of the central nervous system (Finkel et al., 2009; Forman, 2011). Etomidate has a good hypnotic effect but less analgesic and muscle relaxation efficacy with little to negligible effect on the cardiovascular system (unlike ketamine) so it is used for cardiac and vascular surgeries (Finkel et al., 2009; White and Trevor, 2009; Forman, 2011). Etomidate has a side effect by maintaining the sympathetic outflow (Ebert et al., 1992) besides the suppression of the adrenal gland cortex (Jabre et al., 2009) and causing cognitive deficits as found in a rat model (Dixon et al., 2003). Furthermore, xylazine considered to have analgesic and sedative effects as well as muscle relaxant effect which results from its action by stimulating α_2 -adrenoceptor causing an inhibition of the release of noradrenaline neurotransmitter and leading to depression of the central nervous system. Xylazine is used commonly with ketamine to produce balanced anesthesia characterized by good hypnotic, analgesic and muscle relaxant effects (Pawson, 2008; Kleinz and Spence, 2008).

The main goal of this study was to evaluate the anesthetic profile of etomidate (as well as its toxicity and safety) in the chickens and to determine the benefit of xylazine coadministration to enhance its anesthetic duration, efficacy and to reach a state of balanced anesthesia which is characterized by good hypnosis, analgesia, muscle relaxation and hyporeflexia. The above goal is of a major outcome to be applied in the surgical operations and may be substituted the ordinary protocol of ketamine-xylazine combination in animals since the latter combination lack the complete criteria of balanced anesthesia with the presence of cardiovascular side effect of ketamine.

MATERIAL AND METHODS

Birds

7-14 days-old chicks (70 overall chicks were used in this study) of both sexes were used in all the experiments with mean body weights between 0.1–0.15 kg. They retained in 25 chicks per cage at 30–33°C of temperature (which is the optimal temperature at

this age of chicks) besides incessant light and the litter made up of wood shreds. The birds' advent to water and food at will. The dose of etomidate (Hypnomidate 0.2%, Janssen-Cilag Ltd., UK) and xylazine (2%, alfasan, Holland) were diluted with a physiological normal saline solution in 10 ml used to make the desired concentration to be injected in the chicks for each kg of bird mass as intramuscularly (IM) route (10 ml/kg, IM).

For ethical respects, the professional scientific committee of the department of physiology, biochemistry and pharmacology / College of the Veterinary Medicine / University of Mosul agreed and permitted this research for the necessarily utilization of optimal experimental animals.

Determination of the hypnotic ED₅₀ of etomidate in chicks

Hypnotic ED₅₀ value of etomidate was estimated conferring to the up and down mode (Dixon, 1980). First etomidate's dosage of 5 mg/kg, IM depends on an introductory study. The chicks were superintended for two hours to the incidence of the etomidate's hypnosis (lack the righting reflex). The doses of etomidate then would be diminished or augmented 1 mg rely on the incidence or absence of the hypnotic effect in the chicks, respectively (Mousa and Al-Zubaidy, 2019). The ED₅₀ value was calculated as follows:

ED₅₀ value = $xf + Kd$ were:

xf = The last dose used

K = Table's value which extracted from Dixon, 1980 (depend on X and O symbols obtained)

$d = \pm$ in the dosage

The marks elicited by etomidate hypnosis in chicks (during 1-2 min.) were ataxia, recumbency, closed eyelids, loss of righting reflex and the hypnosis characterized by quiet sleep.

Evaluation of acute TD₅₀ of etomidate in chicks

This experiment was conducted also conferring the up and down described before (Dixon, 1980) mentioned above. Rudimentary dosage of etomidate at 20 mg/kg, IM which depends on an initiative procedure. The chicks were watched twenty-four hours aimed at the appearance of etomidate's toxic marks thereafter,

the doses of etomidate should be reduced or amplified 3 mg according to the death presented by etomidate in the chicks. The TD_{50} was calculated from the equation in the same manner as previous experiment.

The toxicity signs observed in the chicks were recumbency, defecation, excitation, paralysis, increased sensitivity to external stimuli, an increase in the wings and leg movements and the outcome was death during 4-8 min.

Estimation of the drug safety indices of etomidate

The ED_{50} and TD_{50} values of etomidate mentioned above were used for the interpretation and extrapolation the drug safety of etomidate through its use in the following equations (Muller and Milton, 2012):

$TI = TD_{50} \setminus ED_{50}$ (The higher the number of TI resulted in means that the drug is safe and vice versa).

$SSM = (TD_1 \setminus ED_{99} - 1) \times 100$ (TD_1 is the minimum dose which produces an adverse effect in 1% of the experimental sample and ED_{99} is the minimum dose required to produce the therapeutic effect in 99% the experimental sample; large SSM value means the drug is safer).

The dose-responsive hypnotic effect of etomidate in chicks

Etomidate's hypnosis (lack the righting reflex) were watched in three groups of chicks (six chicks/dose group) that injected with different doses of etomidate at 4, 8 and 16 mg/kg, IM procured from the hypnotic ED_{50} value of etomidate from the previous experiment in chicks. The onset of hypnosis (indicated by the loss of the righting reflex) was calculated as the time from etomidate injection to the loss of righting reflex. The duration of hypnosis is the time from the loss of the righting reflex till the chick return and corrected their body to normal position while the recovery time was defined as the time between the onset of hypnosis until the chick begin to move and restore the normal activity (Roder et al., 1993; Mousa and Al-Zubaidy, 2019).

Hypnotic and analgesic efficacy of etomidate and the effect of xylazine combination in chicks

A. Effect of xylazine on etomidate hypnosis

Two groups of chicks (6 chicks/group) were used, the first one consisted of etomidate injection alone at 5 mg/kg, IM and the second one composed of injection of etomidate and xylazine at 5 mg/kg, IM for

each drug. The dose of etomidate was selected from the previous two experiments while the dose of xylazine was selected from another study as it resembles the effective dose of xylazine in the chicks (Mousa and Mohammad, 2012a; Mousa et al., 2019). Onset, duration and recovering from hypnosis were written down in two groups for every chick individually.

B. Effect of xylazine on etomidate analgesia

Other chickens of the same groups mentioned above composed of etomidate alone or etomidate plus xylazine were used in this trial. The voltage of electro-stimulator device (Harvard apparatus, USA) that induce nociceptive effect (specified by distress call) was recorded pre- and post-5 minutes of therapy. The proportion of analgesic effect (the number of chicks that show analgesia to total), its volts including voltage (Δ) for every group was also noted (Mousa and Mohammad, 2012b; Mousa, 2014; Mousa, 2019a).

Measurement of plasma glucose, ALT and AST concentrations in the chicks treated with etomidate alone or etomidate plus xylazine

After 2 hours of etomidate injection alone (5 mg/kg) or etomidate plus xylazine (5 mg/kg, IM for both drugs), the blood got from the jugular vein of the neck (6 chicks/group), experiencing centrifugation to gain the plasma which refrigerated pending analysis during 48 hours. The procedure for estimation of glucose concentration (Wotton, 1974), AST and ALT (Yang et al., 2018) concentrations in plasma were analyzed for all the groups mentioned earlier, in addition to the -ve saline control which all analyzed with the specified kit (Biolabo, France) for glucose and liver enzymes by mean of Chemistry Analyzer Smart-150 apparatus (GenoTEK, USA).

Statistical analysis

Parametric data (onset, duration and recovery from hypnosis as well as glucose, ALT and AST concentrations of three groups) were analyzed by analysis of variance (one-way) followed by the LSD, while student T-test implemented to analyze the two groups (onset, duration and recovery from the hypnosis of two groups besides the pre and post-voltage recorded) (Katz, 2011; Petrie and Watson, 2013). The non-parametric outcome (% antinociception) were resolved by the Fisher exact probability and Mann-Whitney-U-test (Δ voltage) (Kvam and Vidakovic, 2007; Katz, 2011). The outcome reflected significantly differs once p was < 0.05 .

RESULTS

Hypnotic ED₅₀ value for etomidate in chicks

The ED₅₀ value of etomidate that generates hypnosis (lack the righting reflex) in 50 % of the subjected chicks was at 4.30 mg/kg, IM as resolved by the up and down technique (Table 1).

Table 1. Etomidate's hypnotic ED₅₀ in the chicks

Parameter	Result
ED ₅₀ value = $xf + K d$	4.30 mg/kg, IM
The extent of the doses applied	4-5 mg/kg
Starting dose	5 mg/kg
Ending dose (xf)	5 mg/kg
± in the dosage (d)	1 mg
Chicks used	5 (XOXOX)*
Starting of hypnosis	1-2 minutes

X: effect (hypnosis), O: no effect (no hypnosis)

*: Symbols (XOXOX) used to extract table value (K) from Dixon, 1980

Acute TD₅₀ for etomidate in experimental chicks

Table 2 exhibits acute etomidate's TD₅₀ value in chicks determined to become 17.90 mg/kg, IM.

Table 2. Determination of acute TD₅₀ of etomidate in chicks

Parameter	Result
Acute TD ₅₀ value = $xf + K d$	17.90 mg/kg, IM
The extent of the doses applied	17-20 mg/kg
Starting dose	20 mg/kg
Ending dose (xf)	20 mg/kg
± in the dosage (d)	3 mg
Chicks used	5 (XOXOX)*
Occurrence of death	4-8 min.

X: effect (death), O: no effect (alive)

*: Symbols (XOXOX) used to extract table value (K) from Dixon, 1980

Drug safety of etomidate as estimated by safety indices

By using the values of ED₅₀ and TD₅₀ of etomidate mentioned above, The TI of etomidate estimated will be 4.

$$TI = TD_{50} \setminus ED_{50} = (17.90 \text{ mg/kg}) \setminus (4.30 \text{ mg/kg}) = 4.16 = \text{approximate to } 4$$

The TI number (4) means that the effective dose (ED₅₀) used of etomidate should be multiplied 4 times to induce the toxic effect of etomidate and kill 50% of the animals (TD₅₀).

In contrast, The SSM estimated from its equation is as follows:

$$SSM = (TD_1 \setminus ED_{99} - 1) \times 100 = (0.358 \text{ mg/kg} \setminus$$

8.514 mg/kg - 1) × 100 = 100 % (The TD₁ and ED₉₉ values were calculated in response to TD₅₀ and ED₅₀ values respectively mentioned above).

The SSM calculated (100%) means that the effective dose of etomidate (ED₉₉) that produces 99 % anesthesia in animals should be increased by 100% (i.e. from 8.514 to 17.028 mg/kg, IM) to kill 1% of the animals (TD₁) and produces its toxic and deleterious effects. Thus the TI and SSM values reflect that etomidate possesses a preferable and had a wide margin of safety.

The dose-response hypnotic effect of etomidate in chicks

Etomidate injection at 4, 8 and 16 mg/kg, IM produces significant narcosis as dosage hooked-on mode. Hypnotic onset (which is the lack of righting reflex) was fast during 1-5 min. while the period of hypnosis was short between 18-43 min. as well as the regaining from the hypnotic effect of etomidate lasts for 28-84 min. which depend on the doses of etomidate (Table 3).

Table 3. Hypnosis (dose-response) of multiple etomidate dosages in chicks

Etomidate (mg/kg, IM)	Hypnosis		
	Onset (min.)	Duration (min.)	Recovery (min.)
4	5.67 ± 1.15	18.00 ± 1.65	28.67 ± 2.00
8	1.33 ± 0.21 *	27.67 ± 2.25 *	43.83 ± 1.90 *
16	1.00 ± 0.00 *	43.83 ± 1.89 * ^a	84.00 ± 6.04 * ^a

The values typify Mean ± Std.E. for 6 chicks per dose group of chicks

*: significantly difference (p < 0.05) from etomidate dosage 4 mg/kg, IM

*^a: significantly difference (p < 0.05) from etomidate dosage 8 mg/kg, IM

Effect of xylazine on anesthetic efficacy of etomidate in chicks

A. The Effect of xylazine on hypnosis produced by etomidate

The combination composed of etomidate at 5 mg/kg, IM and xylazine at the same dose, shortened the onset of hypnosis and significantly prolong its period as well as there was a significant increase in the regaining time from the hypnotic effect when compared with the group that receives etomidate alone (Table 4-A).

Table 4-A. Etomidate's hypnotic effect alone or with xylazine in chicks

Groups	Hypnosis		
	Onset (min.)	Duration (min.)	Recovery (min.)
Etomidate alone (+ve control)	1.67 ± 0.33	32.67 ± 1.91	51.33 ± 2.93
Etomidate and xylazine	1.00 ± 0.00	59.00 ± 2.93 *	86.83 ± 4.82 *

The values typify Mean ± Std.E. for 6 chicks per group of chicks
Etomidate treatment at 5 mg/kg, IM with or without xylazine at 5 mg/kg, IM
*: significantly difference (p < 0.05) from etomidate alone

B. The Effect of xylazine on analgesia produced by etomidate

The 5 min. recording of the analgesic effect pre-injection of etomidate and xylazine combination denotes that there was a significant increase in the antinociceptive efficacy in comparison to the group that

treated with etomidate alone. At a similar moment, a significant rise in the proportion of analgesic efficacy and a significant increase in the voltage (delta) that produces nociception in comparison to the group that injected with etomidate alone (Table 4-B).

Table 4-B. Etomidate's analgesia alone or with xylazine in the chicks

Variables	Antinociception %	Pre-treatment (Volts)	Post-treatment (Volts)	Voltage (delta)
Etomidate alone (+ve control)	50	6.00 ± 0.45	11.00 ± 2.65	5.00 ± 2.42
Etomidate and xylazine	100 *	7.00 ± 0.52	23.00 ± 0.82 *+	16.00 ± 1.06 *

The values typify Mean ± S.E. for 6 chicks per group of chicks
Nociception induced by electro-stimulation (registered pre- and post 5 minutes) of etomidate therapt (5 mg/kg, IM) with or without xylazine (5 mg/kg, IM)
*: significantly difference (p < 0.05) from etomidate alone
+: significantly difference (p < 0.05) as of volts (pre-treatment) in the same group of chicks

Determination of plasma glucose, ALT and AST concentrations in the chicks treated with etomidate alone or etomidate plus xylazine

Table 5 revealed that there is no significant difference in plasma glucose, ALT and AST concentrations

between groups that received normal saline (-ve control), etomidate alone (+ve control) and that treated with etomidate plus xylazine at 5 mg/kg, IM for each drug.

Table 5. Plasma glucose, ALT and AST concentrations in chicks treated with etomidate alone or etomidate plus xylazine

Groups	Glucose concentration (mg/dl)	ALT (U/L)	AST (U/L)
Normal saline (-ve control)	133.32 ± 11.93	15.35 ± 2.10	114.00 ± 5.51
Etomidate alone (+ve control)	135.67 ± 14.97	18.37 ± 2.19	104.10 ± 4.71
Etomidate and xylazine	142.67 ± 10.24	14.93 ± 1.12	111.73 ± 2.55

The values typify Mean ± Std.E. for 6 chicks per group of chicks
Etomidate and xylazine were injected at 5 mg/kg, IM for each drug

DISCUSSION

The main goal of this study was to evaluate the anesthetic profile of etomidate in the chickens and to determine the benefit of xylazine coadministration to enhance its anesthetic duration, efficacy and to reach a state of balanced anesthesia which is characterized by good hypnosis, analgesia, muscle relaxation and hyporeflexia. The mentioned goal is of a major and valuable outcome to be applied in the surgical operations and may be substituted the ketamine-xylazine combination in animals since the latter combination lack the complete criteria of balanced anesthesia with the presence of cardiovascular side effect of ketamine. Etomidate is considered a general anesthetic agent that produces rapid induction with a short duration of anesthesia by its potentiation of the GABA neurotransmitter and GABA_A receptor effect, causing an inhibition of the nervous system. Etomidate has a good hypnotic effect but less analgesic and muscle relaxation efficacy with little to negligible effect on the heart and circulation so it is used for cardiovascular surgeries (Finkel et al., 2009; White and Trevor, 2009; Forman, 2011) though, etomidate is considered a safe drug of choice for using in anesthesia in human because it possesses many advantages including a well-known mechanism, protection from myocardial and cerebral ischemia, decreasing histamine release with a uniquely stable hemodynamic status (Bergen and Smith, 1997; Vinson and Bradbury, 2002; Falk and Zed, 2004; Forman, 2011), has a neuroprotective efficacy on the nervous system in contradiction of the diabetic oxidative injury (Ates et al., 2006) and was found to have efficient anesthesia than pentobarbital (Baxter et al., 2007). In response, the values of TI and SSM calculated in this study refers that the etomidate is safe and possesses a wide margin of safety (Janssen et al., 1975; Forman, 2011). Furthermore, xylazine preferred to use commonly with anesthetic agents like ketamine to produce balanced anesthesia characterized by worthy hypnosis, analgesic and muscle relaxant properties because it possesses analgesic, sedative, and muscle relaxant efficacy that are resultant from its action on α_2 -adrenoceptor (Paw-

son, 2008; Kleinz and Spence, 2008). The result of this study clarifies the anesthetic profile of etomidate in the chicks through determining the hypnotic ED₅₀ and acute TD₅₀ values as well as by evaluating the hypnotic dose-response fashion for etomidate which came close and in accordance to what's found in other laboratory animals (Janssen et al., 1975). As found in this study, etomidate when combined with xylazine, produce balanced anesthesia. That etomidate-xylazine combination enlarged the hypnotic effect and increased the analgesic efficacy as well as a decrease in the doses of both agents with minimizing the side effects of both drugs when compared with etomidate alone and it is typically of beneficial value for use in surgeries and may replace the classical remedy of ketamine-xylazine combination. The interaction between etomidate and xylazine may be regarded as their synergistic inhibition of the various areas of the brain with different mechanisms of action on their receptors. Xylazine alone was known to cause an increase in plasma glucose concentration, as a side effect, due to its mechanism of action (Roder et al., 1993). Neither etomidate alone, nor etomidate plus xylazine differ significantly from the negative control (saline group) concerning plasma glucose, ALT and AST concentrations as showed in this study that came close to the normal concentration ranges in chickens of another study (Cruz et al., 2018) and the reason may be attributed to their single and small doses of each drug used for a short period of time and the short time for plasma estimated suggesting another reason for using this combination for inducing prolonged anesthesia in the chicks.

CONCLUSIONS

The results of this study propose the likelihood of using etomidate as an anesthetic agent for short surgical trials in the chickens that can be more effective by using xylazine to yield balanced anesthesia (characterized by good hypnosis and analgesia) without causing significant side effects; supplementary studies are required in other animal species.

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CONFLICT OF INTEREST

None declared by the author.

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