بسم الله الرحمن الرحيم

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Profile of ketamine and combination of ketamine-xylazine in domestic fowl *(Gallus domesticus)*

إعطاء الكيتامين هيدروكلورايد والكيتامين والزيلازين كمخدرات في الكتاكيت

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صدق الله العظيم

DEDICATION

We dedicate this work

To our fathers and mothers

To our Sisters and brothers

To any one supported us in any way throughout this work.

To our collage, collage of veterinary medicine.

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We would like to express our gratitude for everyone who helped us in our research with endless thanks for our supervisor ***Prof. Ahmed Abdallah Sanhouri*** *who did not keep any effort in encouraging us to do a great job, providing our group with valuable information and advices to be better next time.*

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To ***Director and staff of Inmaa company of poultry.***

Abbreviations

Abbreviation	Meaning
I/M	Intramuscular
g	Gram
Kg	Kilogram
I/V	Intravenous
Sec	Second
Min	Minute
P	Page
G	Guanine protein

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ABSTRACT

Ketamine hydrochloride was tested as a general anesthetic (I/M) injected at a dose rate of (1.49 mg/kg) the dose was chosen according to the equation (y=9.5x±34) obtained by Elowni and Sanhouri et al., (2018) to 3-days old domestic fowl (*Gallus domesticus)* numbers of birds 5 in each group of study. The time for onset of anesthesia: mean ± standard deviation 31 ± 37.28 seconds, stable anesthesia: mean ± standard deviation 21 ± 6.28 minutes, compared to onset of anesthesia in Ketamine (60mg/kg), in the quail (*Coturnix coturnix)* mean ± standard deviation 7 ± 1.56minutes and the duration of anesthesia 44.1±12.99minutes respectively. In another experiment xylazine was used at doses of 2.5, 1, 0.5(mg/kg) . The time for onset of anesthesia: mean ± standard deviation 42.40 ± 22.75seconds for (2.5 mg/kg), 56.40 ± 33.20seconds for(1mg/kg) and 21.40 ± 24.96seconds for(0.5mg/kg) compared to 9.7±2.11 minutes for the quail study(18mg/kg). The time for duration of anesthesia: mean ± standard deviation 83 ± 15.46 for (2.5 mg/kg), 50.40 ± 10.35 for (1mg/kg), and 18±1.58 for (0.5mg/kg), compared to the quail study (using xylazine,18mg/kg) mean ± standard deviation 40.8±3.9 minutes. Ketamine + Xylazine (30mg/kg, 9mg/kg), the onset: mean ± standard deviation 1.9 ± 0.53 minutes. The stable anesthesia mean ± standard deviation 77.8 ± 18.62, (Durrani and Mohammed et al., 2014). The combination of Ketamine at dose rate of 2.5mg/kg ad Xylazine 0.8 mg/kg in our study resulted in 100% mortality and this in contrast to the study of Durrani and Mohammed et al., (2014) in quail (*Coturnix coturnix*). The difference could be attributed to the age of the birds and the dose level. Further work is eminent to through some light on the combination of Ketamine and Xylazine in the domestic fowl (*Gallus domesticus).*

Key words: Ketamine, Xylazine, Xylazine-Ketamine combination, anesthetics, fowl.

ملخص البحث

تم إختيار جرعة الكيتامين حسب المعادلة ص=9.5س+34 المستخلصة من دراسة سابقة للعوني, سنهوري وآخرين (2018) وكانت الجرعة (1.49 ملغ/كلغ) في الكتاكيت عمر ثلاثة ايام بعدد 5 كتكوت لكل تجربة بالحقن في العضل. وكانت النتائج شبيهة بعض الشئ بالدراسة السابقة حيث حصلنا على زمن تخدير (31-16) دقيقة مقارنة مع اربعون دقيقة في الدراسة السابقه. وكان الزمن الإبتدائي من إعطاء المخدر وحتى ظهور التخدير الحقيقي 37.29±31 ثانية مقارنة مع 1.56±7 دقيقة في طيور الكويل البالغة ومكتملة النمو بجرعة (60 ملغ/كلغ) وزمن التخدير الحقيقي(12.99±44.1). وفي تجربة أخرى أستعمل الزيلازين كمخدر ومزيل للألم بجرعات (2.5 ملغ/كلغ), (1 ملغ/كلغ), (0.5 ملغ/كلغ) على التوالي وكانت النتائج مماثلة نوعا ما لدراسة طائر الكويل البالغ وكان زمن التخدير (15.56±83), (10.35±50.40) و (1.58±18) دقيقة على التوالي مقارنة (40.8±33.99) دقيقة وجرعة الزيلازين (18 ملغ/كلغ) وفي تجربة أخرى إستعملنا الكيتامين + الزيلازين وكانت النتائج نفوق 100%. وعليه يجب إجراء تجارب أخرى مستقبلية للوقوف على الجرعات المناسبة من الكيتامين + الزيلازين في الطيور المنزلية.

INTRODUCTION

General anaesthesia in birds can be accomplished with either injectable or inhalant anaesthetic agents (Sedgwick ,1989).Avian respiratory system consist of two separate distinct functional components: one- for ventilation, conducting airway, air sacs, thoracic skeleton and muscles of respiration, and the other component for gas exchange includes: parabronchial lung(Ludder and Matthews 1996), whereas these two components proved useful with injectable anaesthetics , they were un useful when using inhalational anaesthesia (Mclelland,1988). However, the advantage of having the trachea in complete rings applied to great deal with inhalational anaesthesia rather than injectable (McLellan ,1989).

Injectable anaesthetics are used frequently to produce anaesthesia in birds and they have the advantages of low cost, ease of use, rapid induction of anaesthesia and no records of pollution of the working environment. However, there are disadvantages associated with their use including significant variation between species and individual in term of dose and response, ease in overdosing by any route and difficulty to maintain surgical anaesthesia without severe cardiopulmonary depression. Recovery may be prolonged and of untoward effects (Franchetti and Klide, 1978).

Injectable drugs such as ketamine, diazepam, xylazine, have been used to induce anaesthesia of relative short duration in variety of bird's species (Franchetti and Klide,1978).

Ketamine is a dissociative anaesthetic with anaesthetic properties. It is administered intravenous or intramuscular to avian species. In most instances, however, the drug is used in combination with other injectable agents to reduce or eliminate many of the undesirable side effects if used alone. The drug is recommended for use in a wide range of avian species (Little, 1971; Flecknell, 2009). Inhalant anaesthetics especially Isoflurane are considered the anaesthetic of choice for birds, ketamine is used as induction agent for general anaesthesia which is maintained by inhalational anaesthesia in other species, (Ludders and Matthews, 1996). Advantages including rapid induction and recovery,

especially when inhalant anaesthetic with low blood-gas solubility are used, easier control of anaesthetic depth. Disadvantage is that delivery of potent inhalant requires special equipment such as source of oxygen, vaporizer, breathing circuit and mechanism for scavenging waste anaesthetic gases and it is expensive.

Objectives of study: -

1. To observe the onset of ketamine and xylazine and main clinical signs.
2. To investigate duration of ketamine, duration and toxicity of xylazine alone and xylazine with ketamine.

Chapter one

Literature review

1.1. Ketamine Hydrochloride

Ketamine produces a state of catalepsy and can be given by any parenteral route. Doses range from 10 to 200 mg/kg, depending on species and route of administration. Drugs such as diazepam or xylazine have been combined with ketamine in order to prolong or improve the quality of anaesthesia, to provide muscle relaxation, or to provide additional analgesia. When used alone, ketamine is suitable for chemical restraint for minor surgical and diagnostic procedures, but is not a suitable general anaesthetic for major surgical manipulations. Higher doses of ketamine only serve to prolong its action while decreasing its margin of safety (McGrath et al., 1984).

1.2. Ketamine Hydrochloride in bird

Injectable anaesthetics that mostly have been used in birds were combination of ketamine and xylazine, however combination of ketamine and diazepam is less frequently used. Ketamine produce cataleptic state that inhibits movement, but doesn't provide adequate analgesia for major surgical procedures. (Harrison, 1985 and Mandsager, 1989).

Commercial name of ketamine hydrochloride:
Ketalar®, ketalin®, ketalor® and ketaminol®.

Chemical name of ketamine hydrochloride:

2- (2-Chlorophenyl)-2- (Methyl amino).

Ketamine hydrochloride formula:

Free base: C13H16C1NO

Hydrochloride Salt: C13H17C1NO.

1.3. Usage of Ketamine Hydrochloride in birds:

Ketamine is used as intravenous injectable anaesthetic.

1.4. Side effects of ketamine hydrochloride:

Emergency delirium, nightmares and hallucinations, Hypertension and tachycardia, Prolonged recovery, Salivation, Increased intracranial pressure, Allergic reactions. (Aitkenhead, Rowbotham,.et.al, 2001).

Complex reaction to the brain depressant at certain area and stimulating other, which enables it to anesthetise and cause seizure in overdose (Haskins, 1995).

1.2. Xylazine:

An a2-adrenergic agonist with sedative and analgesic properties, has been used for minor surgical and diagnostic procedures (Ludders and Nora,1996).

Commercial name of xylazine:

Xyla®, Xylaject®

1.2.1. Pharmacology of xylazine:

Xylazine is an alpha2-adrenergic agonist it decreases release of neurotransmitters from the neurons. It also decreases transmission via binding to presynaptic Alpha2-receptors (negative-feedback receptors). The result is decreased sympathetic outflow, analgesia, sedation, and anaesthesia (Mark,2016). Within the central nervous system, activation of a-2adrenoreceptor induces analgesia and sedation, these result from binding of xylazine to the a2adrenoreceptor in presynaptic membrane results in activation of membrane associated with G-protein and this leads to activation of potassium channels in the post synaptic neurons, causing the cells to lose potassium and becomes hyperpolarized, this action makes the cell unresponsive to the excitatory input (Thurmon et al.,1996).

1.2.2. Pharmacokinetic of xylazine:

Absorption: - xylazine is rapidly absorbed following I/M administration.
Distribution: - rapidly distributed following I/V injection, xylazine perfuse to target organs such as heart, lung, liver and kidney.

Metabolism: - rapidly metabolised in liver, Excretion: - through the kidney (Salonen,1992).

1.2.3. Usage of xylazine in birds:

It has been used as sedative, analgesic, and muscle relaxant (Greene., *et.al*, 1988).

1.2.4. Side effects of xylazine:

Xylazine can cause respiratory depression, excitement, and convulsions (Samour et al., 1984). Hypoxemia and hypercapnia (Ludderset al., 1989). It frequently causes salivation, muscle tremor convulsions, sometimes aggravated by noise (Bob Doneley, 2016).

It has profound cardiopulmonary effects, including second-degree heart block, Brady arrhythmias, and increased sensitivity to catecholamine-induced cardiac arrhythmias (Ludders and Nora,1989).

1.2.5. Recovery

Is prolonged, but xylazine can be reversed by Atipamezole (Allen and Oosterhuis,1986)

1.3. Combination of xylazine and ketamine

Synergism between xylazine and ketamine lead to good quality of anesthesia and analgesia of longer duration than the use of ketamine alone, use of combination give smooth induction and recovery accompanied by deep analgesia and muscle relaxation (Ludders, et al, 1989).

The combination can be associated with cardiac arrhythmias and hypotension.

Chapter Two

Materials and methods

2.1. Birds selection

Twenty-five birds - three days old of Leghorn chick, of both sexes were used, their body weight ranged from 32 – 38g, digital balance was used to determine the body weight of the chickens.

2.2. Experimental design

Water and food of all birds were withheld one day prior to drug administration. The study was conducted on 25 birds that were randomly divided into 5 groups respectively, each group contain five birds, the area of injection (pectoral muscle) was disinfected with alcohol.

Drugs used for anesthesia were ketamine (Rotex medica, Ketalar, concentration5%) xylazine (inter chemical, Xyloject, concentration 2%).

The first group of birds received ketamine I/M at dose rate 1.49mg/kg, insulin syringes were used for injection and normal saline for dilution, second, third and fourth groups of birds received dose of xylazine administered I/m in pectoral muscle at 2.5, 1, 0.5mg/kg dose rate respectively, the last group received combination of xylazine and ketamine (0.8mg/kg,2.5mg/kg) respectively.

2.3. Onset of anesthesia

Measured by time of administration of the anaesthetic drug until the bird fall down.

2.4. Duration of anesthesia

Was recorded for individual bird in each group treated with different dose and grouped together at ± standard deviation for different groups, measured from time of onset of anesthesia until the bird was fully awake.

2.5. Statistical test

The data were analysed with anova test used spss programme version 18.

Chapter Three

Results

Ketamine (1.49mg/kg). The result depicted in table(1a), the onset of anesthesia ranged from 1 to 90 seconds at the above mentioned dose. Stable anesthesia ranged from 16 minutes to 31 minutes, mean ± standard deviation 22.00 ± 6.28 table (1).

Xylazine(2.5mg/kg), (1mg/kg), (0.5mg/kg), the onset of anesthesia ranged from 56.40 ± 33.20 to 21.40±24.96 seconds, results shown in table (1) the time varied between the groups according to the dose and response. The same groups showed (results depicted in table2) for stable anesthesia a range from 83±15.46 to 18±1.58 minutes for all the above mentioned groups, also depending upon dose level. The dose and response were positively correlated.

Ketamine(2.5mg/kg) + xylazine(0.8mg/kg)

Results were shown in table (2) onset of anesthesia 19.80 ± 13.42 seconds with minimum value of 4 to maximum value of 39 seconds.

Actually all the birds in this group showed signs of toxicity and did not recover at all.

Table (1)

Number of chicks	**1**	**2**	**3**	**4**	**5**
Onset of anesthesia in seconds	**4**	**1**	**45**	**15**	**90**
Duration of anesthesia in minutes	**26**	**31**	**19**	**16**	**18**

This table shows the onset and duration of anesthesia for ketamine (1.49mg/kg)

Table (2) Descriptive

Onset of anaesthesia in seconds

	N	Mean ± standard deviation	Std. Error	Minimum	Maximum
Ketamine group (1.49mg/kg)	5	31.00 ± 37.289	16.676	1	90
Xylazine (2.5mg/kg)	5	42.40 ± 22.755	10.176	21	73
Xylazine (1mg/kg)	5	56.40 ± 33.201	14.848	18	98
Xylazine (.5mg/kg)	5	21.40 ± 24.966	11.165	2	60
Ketamine + xylazine (2.5mg/kg,.8mg/kg)	5	19.80 ± 13.424	6.003	4	39

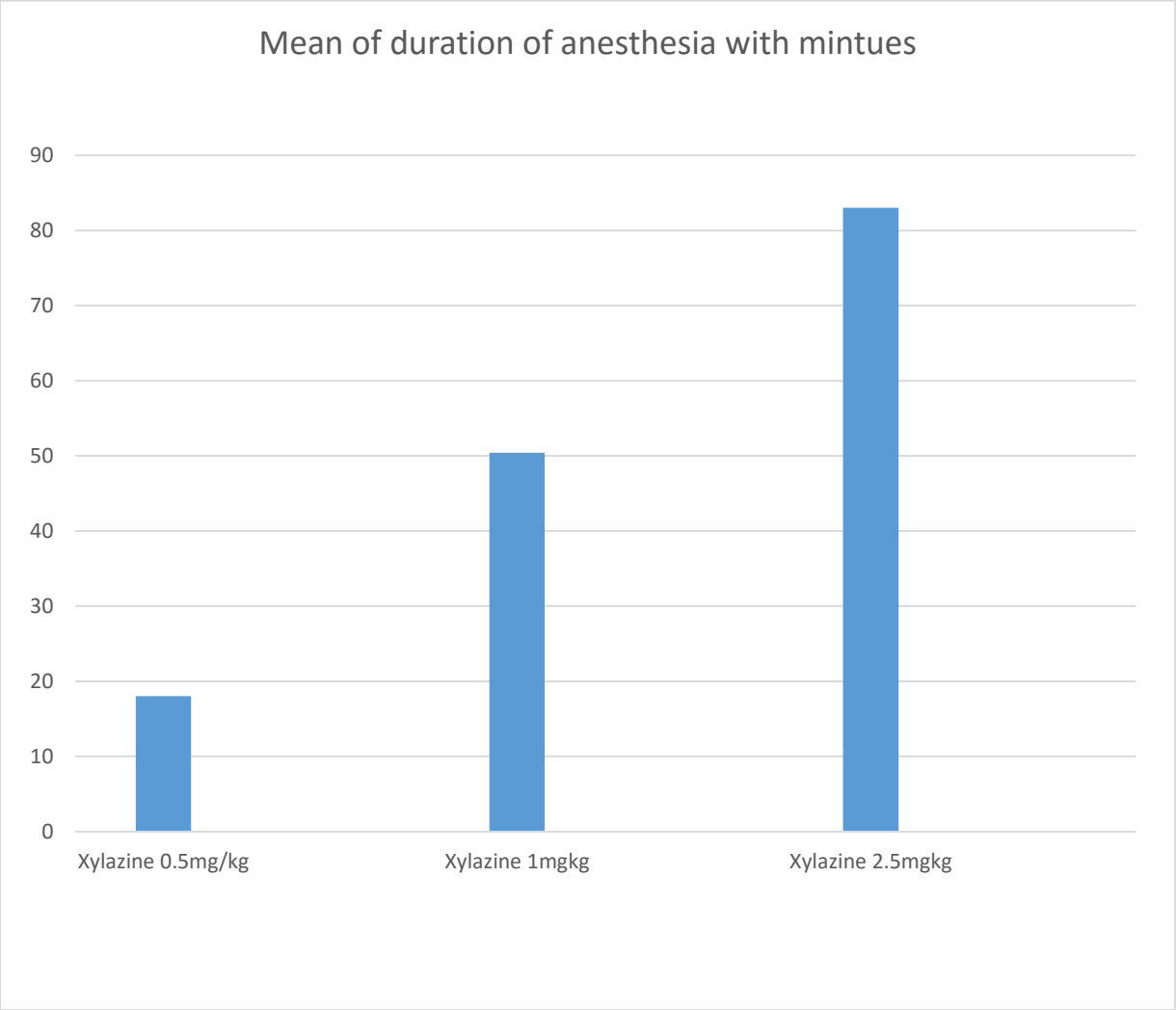
Table (1) shows the descriptive statistics (size of the sample, mean and standard deviation, minimum and maximum value) for onset of anesthesia in seconds.

Table (3) Descriptive

Duration of anesthesia in minutes

	N	**Stable anesthesia (mean ± standard deviation)**	**Std. Error**	**Minimum**	**Maximum**
Ketamine group (1.49mg/kg)	5	22.00 ± 6.285	2.811	16	31
Xylazine (2.5mg/kg)	5	83.00 ± 15.460	6.914	70	104
Xylazine (1mg/kg)	5	50.40 ± 10.359	4.632	38	63
Xylazine (.5mg/kg)	5	18.00 ± 1.581	.707	16	20
Ketamine + xylazine (2.5mg/kg,.8mg/kg)	5	23.00 ± 1.581	.707	21	25

Table (2) shows the descriptive statistics (size of the sample, mean and standard deviation, minimum and maximum value) for duration of anaesthesia in minutes.



Means Plots

The above graph shows the means for the samples

Chapter Four

Discussion

The dose for ketamine 1.49mg/kg was actually chosen according to the study of Elowni and Sanhouri *et al.,* (2018) to give stable anesthesia for 40 min, Y=9.5x+34, however the maximum anesthesia obtained was 31 min, the variation could be attributed to the wide range of individual variations (Franchetti and Klide,1978),The results obtained was similar to that of Durrani et al.,(2014), they used 60mg/kg ketamine alone with an onset of 7±1.56 min compared to 31±37.28 sec and stable anesthesia of 44.1±12.99 min, in our study the time for stable anesthesia was 22±6.28 min the difference related to species difference or the age of the birds. Xylazine at 2.5mg/kg gave onset of anesthesia of 40.40 ± 27.75 to 21.40 ± 24.966 seconds in the group received 0.5mg/kg. The stable anesthesia was positively correlated at 2.5mg/kg and showed the longest time of all the groups, and lower value obtained was 18 ± 1.581 minutes for the group received 0.5mg/kg. The stable anesthesia was actually free of any untoward effects or any other disturbances. The recovery time was also free of any rough time and the birds could tolerate the anesthesia at all dose given.

Parenteral injection of xylazine alone at the dose level of (2.5mg/kg), (1mg/kg) and (0.5mg/kg) produced safe, light but smooth sedation and analgesia. However, higher doses of xylazine produced deep sedation, leading to unconsciousness and a light plane of anesthesia. In study of Durrani *et al.,* (2014). Xylazine with a dose rate of 18mg/kg in the quail (*Conturnix conturnix)* their onset was 9.7 ± 2.11 min compared to 42.40 ± 22.75 sec, for 2.5mg/kg, and 56.40 ± 33.20 seconds for 1mg/kg, and 21.40 ± 24.96 sec for the dose rate 0.5mg/kg. And the duration of anesthesia or deep sedation in their study was 40.8 ± 33.99 min compared to 83 ± 15.46 min for (2.5mg/kg), and 50.40 ± 10.35 min for (1mg/kg), and 18 ± 1.58 min for (0.5mg/kg).

Xylazine (0.8mg/kg) as an alpha-2 agonist in combination with ketamine (2.5mg/kg) produced profound deep anesthesia, with 100% mortality, the results obtained was to some extent contradictory to the results of Durrani and Mahmoud et al., (2014) in their study they used xylazine (9mg/kg), ketamine (30mg/kg), the difference could be attributed to the fact that they used adult quails (*Conturnix conturnix)*, and in our study we used very young chicks 3 days old , (*Gallus domesticus*) further investigation is definitely needed with either change of dosage in young chicks or with the adult chicks of the same type to highlight the effect of xylazine and ketamine in a better way.

Conclusion

It is concluded that ketamine, when given I/M can be used effectively and safely as general anaesthetic to domestic fowl 3 days old, xylazine could be used alone for minor procedures which necessitate the birds to sleep for a duration of 83 minutes.

Recommendations

We do not recommend the use of the doses level of ketamine-xylazine

(2.5mgkg, .8mg/kg) respectively in 3days old chicks, however, further studies were needed to throw some light on the level of the effective safe dose from the above combination for both young and adult fowl in future studies.

Appendix

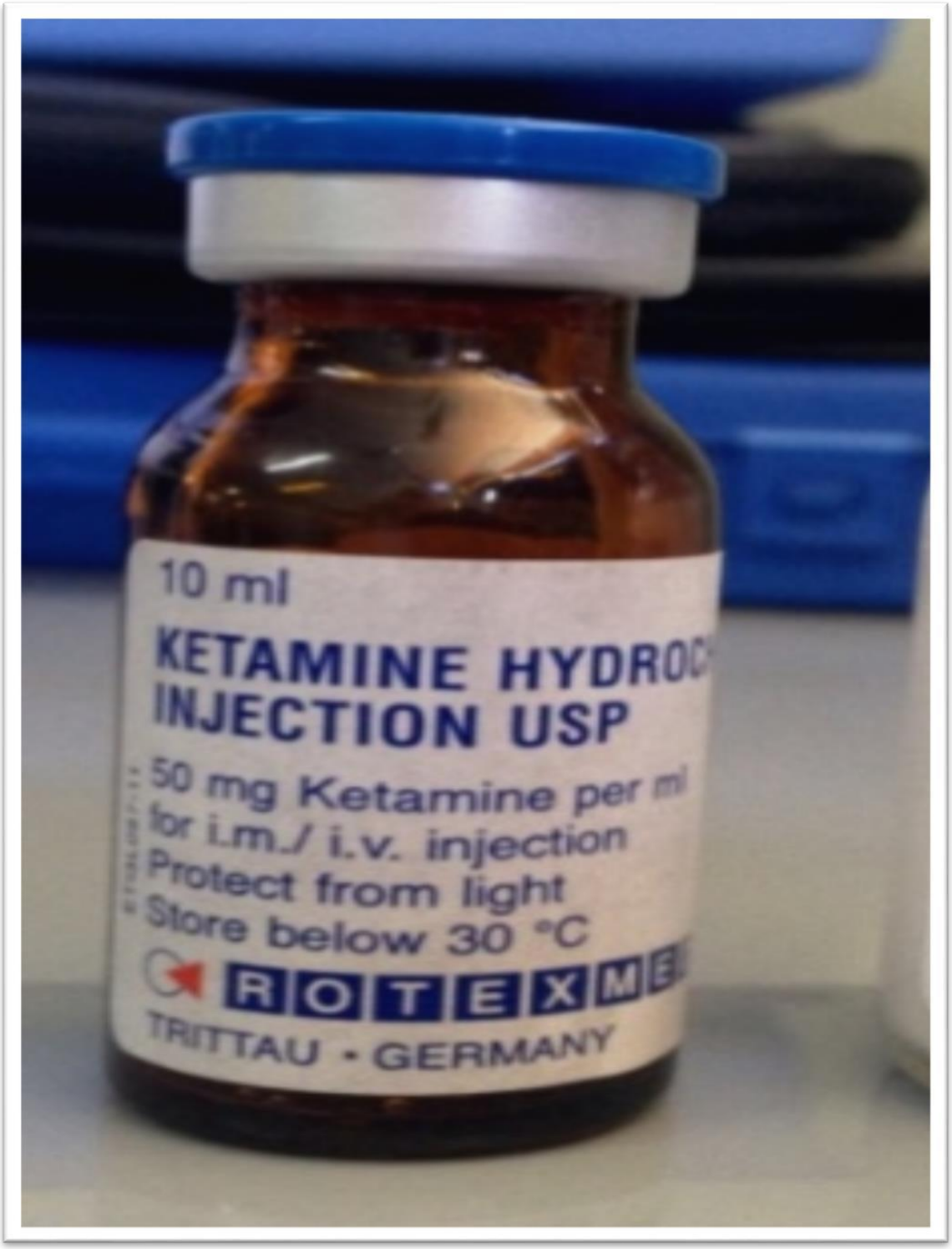


Figure no.1

Ketamine hydrochloride injection

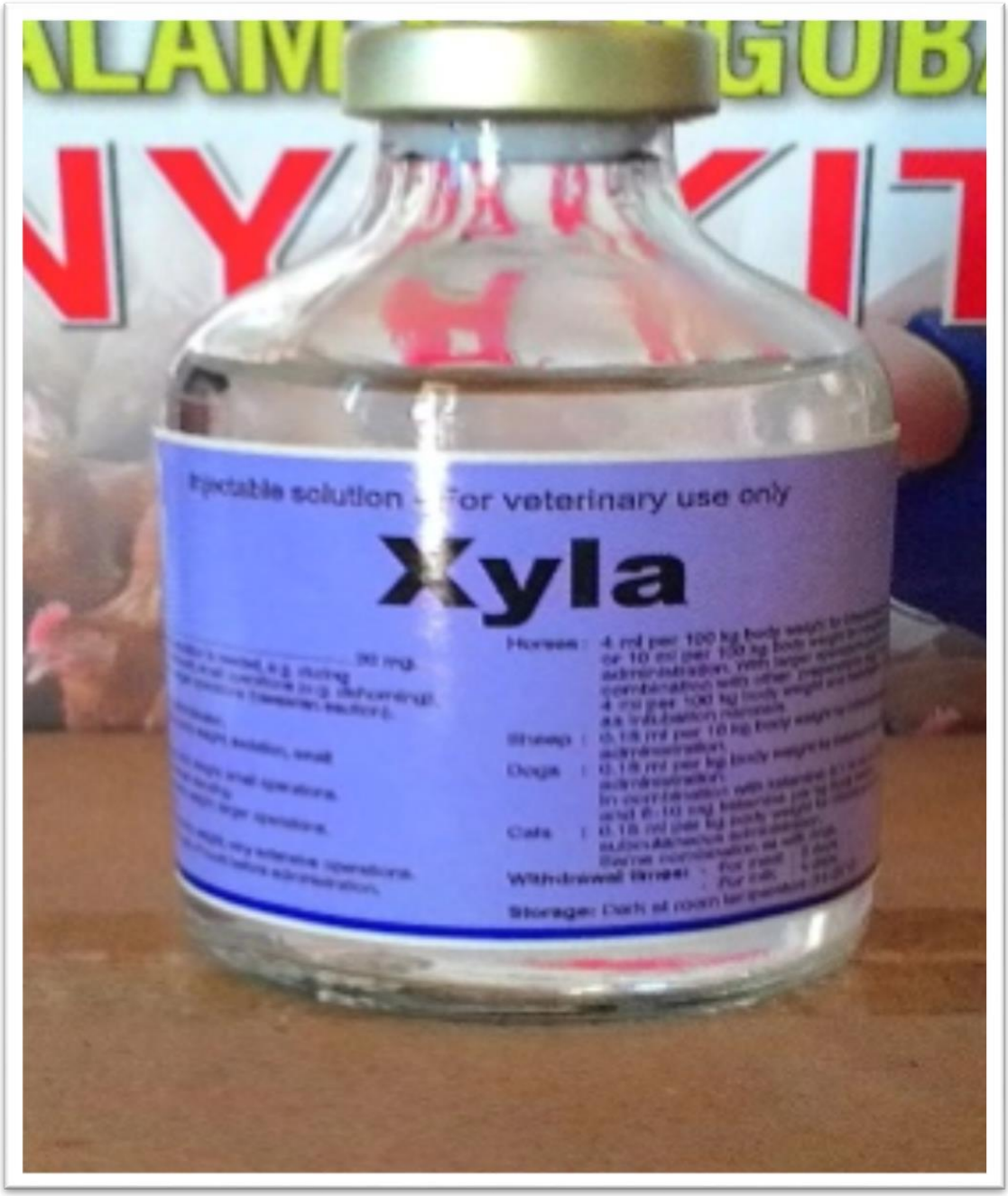


Figure no.2

Xylazine hydrochloride

Figure no.3

Digital balance

Figure no.4

A dose of combination of ketamine (2.5mg/kg) and xylazine (0.8mg/kg) lethal to the birds

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