بسم الله الرحمن الرحيم

SUDAN UNIVERSITY OF SCIENCE AND TECHNOLOGY

COLLEGE OF VETERINARY MEDICINE

Administration of Ketamine Hydrochloride as General anesthesia in Domestic Fowl

اعطاء الكيتامين هيدروكلوريد كمخدرعام في الدجاج

A Dissertation Submitted in Partial Fulfillment of the Requirements of College of Veterinary Medicine for B.V.M

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{ يَرْفَعِ اللَّهُ الَّذِينَ آمَنُوا مِنكُمْ وَالَّذِينَ أُوتُوا الْعِلْمَ دَرَجَاتٍ}

[المجادلة: 11]

{ وَقُلْ رَب زِدْنِيْ عِلْمَاً }

[طه :114]

" العلم كنــز و الصــدور منـــــازل "

DEDICATION

To the great effort my father made

To my mother who has been there for me all my life

To my brothers and sisters for all their continued support.

ACKNOWLEDGEMENTS

Above all, praise is to my almighty Allah for giving us a good health, wisdom, ability, and strength to carry out this work and for all other graces. We would like to express our deep and sincere gratitude and appreciation to our supervisor Dr: Ahmed Abdallah Sanhouri and Technology for his excellent guidance, support, and constant encouragement throughout this project and also for his invaluable assistance and instructions, without which, it would not have been possible to accomplish this project and for reading and correcting the manuscript. We offer our sincere gratitude also to the teaching staff of the College of Veterinary Medicine, Sudan University of Science and Technology, for their very useful assistance and instructions throughout the five years; from the beginning of our undergraduate study to the end. Finally, We are thankful to our parents, sisters and brothers, And to all our friends and colleagues for their everlasting support**.**

Abbreviations

Abbreviation	Meaning
Mg	Milligram
Kg	Kilogram
Min	Minute
I/M	Intramuscular
I/P	Intraperitoneal
Fig.	Figure
NMDA	N-methyl-D-Aspartate
GABA	Gamma-Amino-butyric-acid
LD_{50}	Lethal dose
Log	Logarithm
G	Gram

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Abstract

Ketamine hydrochloride was tested as a general anesthetic administered as a single intramuscular injection at 2.5, 5, 10 or 30 mg/kg to twenty- 3-day-old chicks and at doses of 20, 30, 60, 175 or 350 mg/kg to twenty- 40-day-old chickens. A dose of 30 mg/kg is lethal to chicks whereas lethality was produced by a dose of 350 mg/kg in older birds. Toxicity of the drug was expressed by the formulae y = 30x-50 for chicks and y = 0.3252x + 0.89 for older birds where y is mortality percent and x is the log dose. The time for onset of anesthesia was 10-60 seconds in chicks compared to 1.0-10.7 minutes in older birds depending upon dose levels. In both occasions, drug dose and response are negatively correlated (y = -25x + 77.33 and y = -2.91x + 10.7, respectively). Stable anesthesia was maintained for 40-60 min in chicks and 20-120 min in older birds. Duration of anesthesia was also a function of dose and they are positively correlated (y = 9.5x +34 and y = 22.18x +4.8, respectively). It is concluded that Ketamine, when given intramuscularly, can be used effectively and safely as a general anesthetic to both young and older chickens. No untoward effects were observed up to 3 weeks when the experiments were terminated.

ملخص البحث

تم اختبار الكيتامين باعتباره مخدر عام يعطي كحقن عضلي جرعة واحدة عند 2.5 أو 5 أو 10 أو 30 ملغم / كغم في عمر 3 أيام (20 كتكوت) للكتكوت وبجرعات من 20 أو 30 أو 60 أو 175 أو 350 ملغم / كغم بعمر 40 يوم (20 كتكوت) .الجرعة من 30 ملغ / كغم هي قاتلة للكتاكيت في حين أن الجرعة 350 ملغ / كغم هي القاتلة في الكتاكيت الكبيرة . تم التعبير عن سمية الدواء عن طريق المعادلة y = 30x-50 للكتاكيت الصغيرة والمعادلة y = 0.3252x + 0.89 للكتاكيت الكبيرة حيث yهي نسبة الوفيات و x هي الجرعة اللوغرثمية.

كان الوقت لبدء ظهور التخدير 10-60 ثانية في الكتاكيت الصغيرة مقارنة 1.0-10.7 دقيقة في الكتاكيت الكبيرة اعتمادا على مستويات الجرعة .في كلتا الحالتين ترتبط جرعة الدواء والاستجابة سلبا (علاقة سلبية) : (y = -25x + 77.33) في الصغيرة و(y = -2.91x + 10.7) في الكبيرة.

تم استمرار التخدير لمدة 40-60 دقيقة في الكتاكيت الصغيرة و20-120 دقيقة فيالكتاكيت الكبيرة. كما كانت مدة التخدير دالة علي الجرعة وترتبط ارتباطا إيجابيا (y = 9.5x +34) و(y = 22.18x +4.8) على التوالي.

ونستنتج أن الكيتامين، عندما يعطى عضليا، يمكن استخدامه بشكل فعال وآمن كمخدر عام لكل من الكتاكيت الصغيرة والكبيرة . لم تلاحظ أي آثار غير مرغوب حتي عمر 3 أسابيع عند نهاية التجارب .

INTRODUCTION

Introduction

Effective or proper general anesthesia is a prerequisite of all major and minor surgeries in birds (Curro,1998). General anesthesia in birds can be accomplished with either injectable or inhalant anaesthetic agents (Sedgwick, 1980). Both of these two procedures have their advantages and disadvantages. Anesthesia induced and maintained by injectable agents is rapid, cheap and need less equipment (Mandelker, 1988).On the other hand, inhalant anaesthetic account for rapid induction and speed of recovery when used (Fedde, 1992).However, with all these benefits, the greatest disadvantage of injectable anesthesiais individual and species variation relative to drug dose and response to specific drug (Paul – Murphy and Fialkowski, 2001).Inhalant anaesthetics are very expensive. In addition they require specialized equipment and well trained staff (Paddlford,1986). Ketamine is a non-barbiturate general anesthetic agent administered most commonly by intramuscular route (I/M) and can also be administered intravenously to produce dissociative anesthesia (Maiti, 2006). It is rarely used alone and it most often used in combination with either xylazine or diazepam. Both xylazine and diazepam produce good muscle relaxation. It has highly variable effect on avian species (Harrison , 1991)..In Sudan, Ketamine is most commonly used because of its availability, relatively low price and achieve good results.

Objectives of the study

1- To observe the onset of ketamine and the main clinical signs.

2- To investigate duration and toxicity of anesthetic drug.

CHAPTER ONE

Literature Review

1.1. Anesthesiain birds

Anesthesia in birds is is ordered by law and necessary for various operations and manipulations. Historically, avian anesthesia has been problem fraught with continuous debate .Many clinician have had their prefer drug "cocktails," and there where many conflicting views with regard to dosage ranges and choice of anesthetic regime. As in other animal species, general anesthesia in bird can be accomplished with either injectable or inhalant anesthetic agent. The goal of anesthetizing of patient is to select the safest drug that allows the minimum amount of physiological change, creats minimal stress in administration, has a high therapeutic index, provides for rapid induction and recovery, provides adequate restraint for the desired procedure and can be safely used in critical cases (Mandsager, 1989).

1.2. Ketamine in poultry

The most commonly reported injectable anesthetics used in birds are combinations of ketamine and xylazine and less frequently, ketamine and diazepam.

Ketamine, a cyclohexamine, produce cataleptic state that inhibits movement, but does not provide adequate analgesia for major surgical procedures. This drug has a highly variable effect in different avian species. It is metabolized by the kidneys and is therefore contraindicated in a patient with renal insufficiency (Harrison, 1985 and Mandsager, 1989).

1.2.1. Administration

The drug can be administerd intramuscularly (most commonly) , and it can be administered intravenously or intraperitoneal.

1.2.2. Duration

The typical duration of anesthesia is 10 to 30 minutes .

1.2.3. Recovery

May take from 30 minutes to several hours, which is completely dose-dependent.

1.3. Pharmacology of Ketamine

1.3.1 Identification

1.3.1.1. Generic name

Ketamine

1.3.1.2. Brand name

Ketalar, Vetalar or Ketaflo

1.3.1.3. Type

Small molecule

1.3.1.4. Chemical formula

C13H16CINO

1.3.2. Description

Cyclohexanone derivative used for induction of the anesthesia.

Its mechanism of action is not well understood, but ketamine can block receptor, N-methyl-D-Aspartate (NMDA receptor).

May interact with sigma receptor (Harrison, 1985).

1.3.3. Indication

For use as sole anesthetic agent for diagnostic and surgical procedure that do not require skeletal muscle relaxation .

1.3.4. Pharmacodynamics

Ketamine is rapid-acting general anesthetic producing anesthetic state characteristic by profound analgesia, normal pharyngeal-laryngeal reflexes, normal or slightly enhanced skeletal muscle tone, cardiovascular and

respiratory stimulation, and occasionally a transient and minimal respiratory depression. The anesthetic state produced by ketamine has been termed " dissociative anesthesia " in that it appears selectively interrupted association pathway of the brain before producing somesthetic sensory blackade.

1.3.5. Mechanism of action

Ketamine has several clinically usefull properties, including analgesia and less cardiorespiratory depressant effectives than other anesthetic agent, it also causes some stimulation of the cardiovascular system. Ketamine has been reported to produce general as well as local anesthesia. Unlike other general anesthetic agents, ketamine does not interact with GABA receptor (Bergman , 1999).

1.3.6. Absorbtion

Rapidly absorbed following paranteral administration.

1.3.7. Metabolism

Hepatic

1.3.8. Side Effects

Ketamine is known to have some undesirabe side effects such as :

- Increase blood pressure (Joly, 1994 and Green, 1996).
- Tremor and vocalisation(Hamza *et al,* 1986).
- Complex reaction to the brain depressant certain areas and stimulating others, which inables it to anesthetize and cause seizures in overdose (Haskins, 1985).

CHAPTER TWO

Materials and Method

Chapter Two

Materials and Methods

2.1. Study area:-

Sudan University of Science and Technology , College of Veterinary Medicine (Hilat Koko) at Banha.

2.2. Experimental birds :-

Twenty 3-day-old Leghorn chicks weighing 45 g, and twenty 40–day-old Ross chickens weighing 860 g of both sexes were used. They were randomly divided into 4 and 5 groups, respectively.

3.3. Anesthetic drug :-

Birds received single injections of Ketamine (Ketamine hydrochloride, "ROTEXMEDICA" GmbH, Trittau, Germany) administered intramuscularly in the pectoral muscle after the injection site had been disinfected with alcohol. Young birds received dose at 2.5,5 , 10 or 30 mg/kg and older groups received 20 , 30 , 60 , 175 and 350 mg/kg.

Onset of Anesthesia: Individual birds treated with different drug doses were observed closely to determine the time for onset of anesthesia measured from the instant of injection of the anesthetic to the moment the bird fell permanently on its side. Mean values were considered for different groups.

Duration of Anesthesia: Duration was recorded for individual birds in groups treated with different doses starting from the time of onset of anesthesia until the bird was fully awake showing normal physical responses. Mean values were considered for different groups.

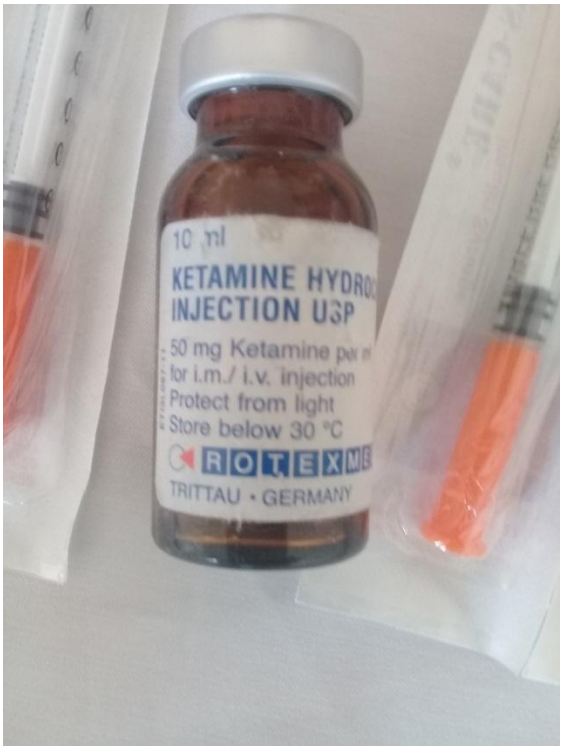

Figure 1 : Ketamine hydrochloride (ROTEXMEDICA GmbH, Taritatu, Germany).

Figure 2 : Digital balance

Figure 3 : 40 -Day-Old Ross Chickens

CHAPTER THREE

RESULTS

Chapter Three

Results

3.1. Three-Day-Old Chicks :-

3.1.1. Drug Toxicity: The intramuscular administration of Ketamine at doses of 2.5, 5 or 10 mg/kg was tolerated by young birds. A dose of 30 mg/kg was instantly lethal to these birds. Logarithmic interpolation (Microsoft Excel) provided the formula y = 30x - 50 (Fig.4) with predicted LD50 3.333 mg/kg.

3.1.2. Onset of Anesthesia: The time varied between 10-60 seconds in different groups depending upon dose level (Fig.5). There was inverse relationship between dose and response (y = -25x + 77.333).

3.1.3. Duration of Anesthesia: Stable anesthesia was maintained for 40-60 minutes also depending upon dose level (Fig. 6). The dose and response were positively correlated (y = 9.5x +34).

3.2. Fourty –Day-Old Chickens :-

3.2.1. Drug Toxicity: The intramascular administration of Ketamine at doses of 20, 30, 60 or 175 mg/kg was tolerated by birds. A dose of and 350 mg/kg was instantly lethal to these birds. Linear interpolation (Microsoft Excel) provided the formula y = 0.325x + 0.89 (Fig.8) with predicted LD50 at 151 mg/kg.

3.2.2. Onset of Anesthesia: The time varied between 40-120 minutes in different groups depending upon dose level (Fig. 9). There was a positive relationship between dose and response (y = -2.91x + 10.7).

3.2.3. Duration of Anesthesia: Stable anesthesia was maintained for 40-60 minutes also depending upon dose level (Fig.10). The dose and response were positively correlated (y = 22.18x + 4.8).

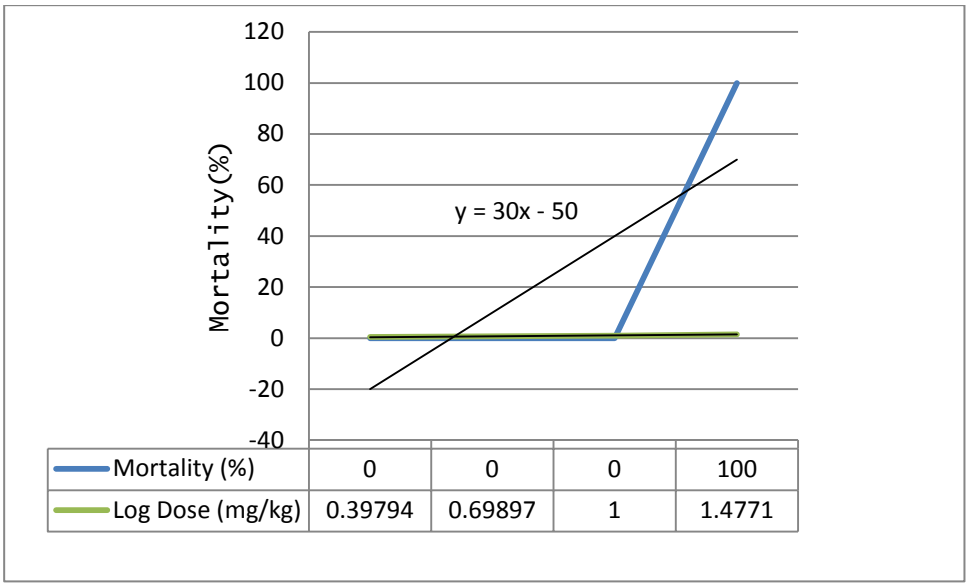

Figure 4: Toxicity of Ketamine Administered Intramuscularly to 3-day-old chicks: Quantal Log-Dose Response Relationship.

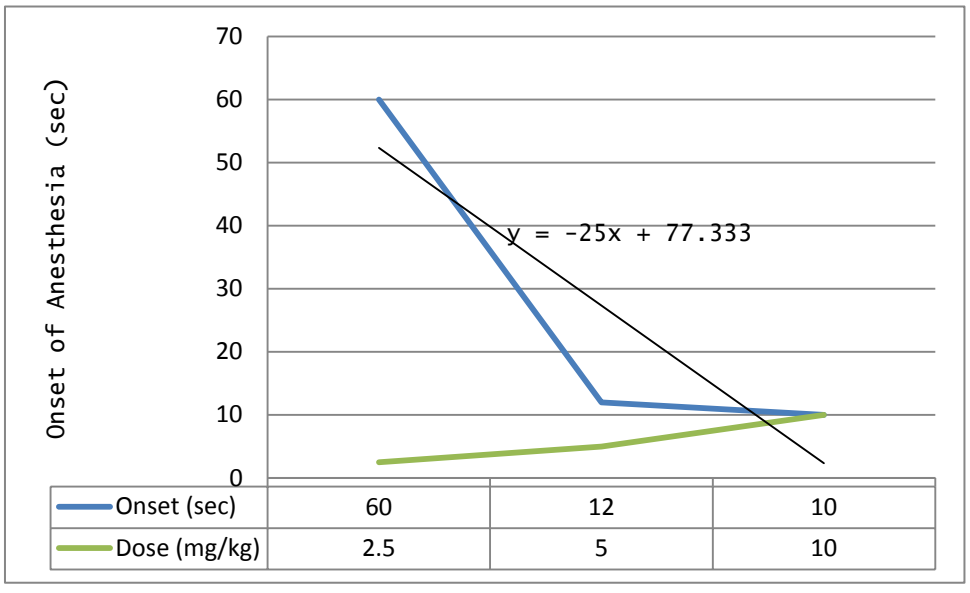

Figure 5: Onset of Ketamine –induced Anesthesia in 3-day-old Chicks

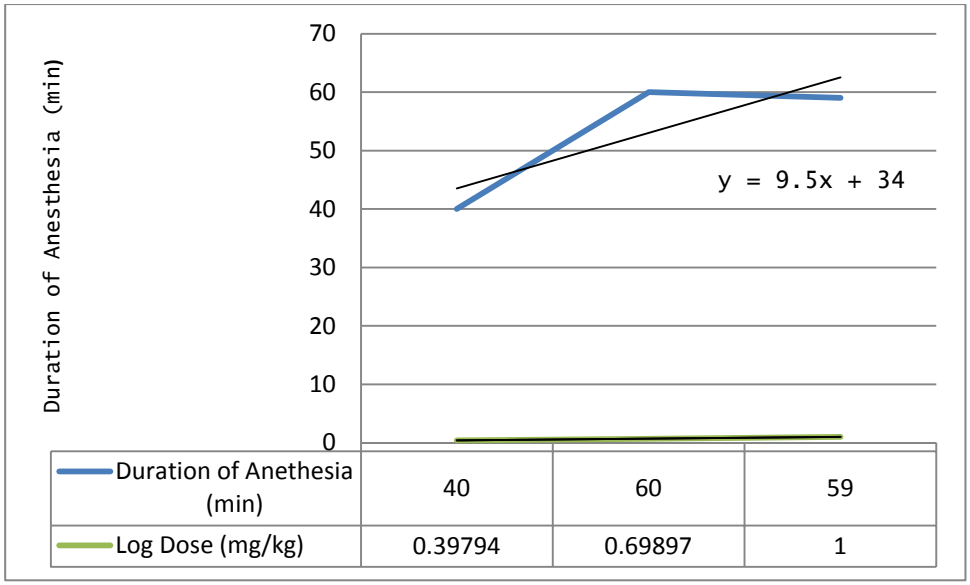

Figure 6: Duration of Anesthesia in 3-day-old Chicks Treated with Ketamine at Different Dose Levels.

Figure 7: A dose of 30 mg/kg was instantly lethal to these birds

Fourty –Day-Old Chickens:-

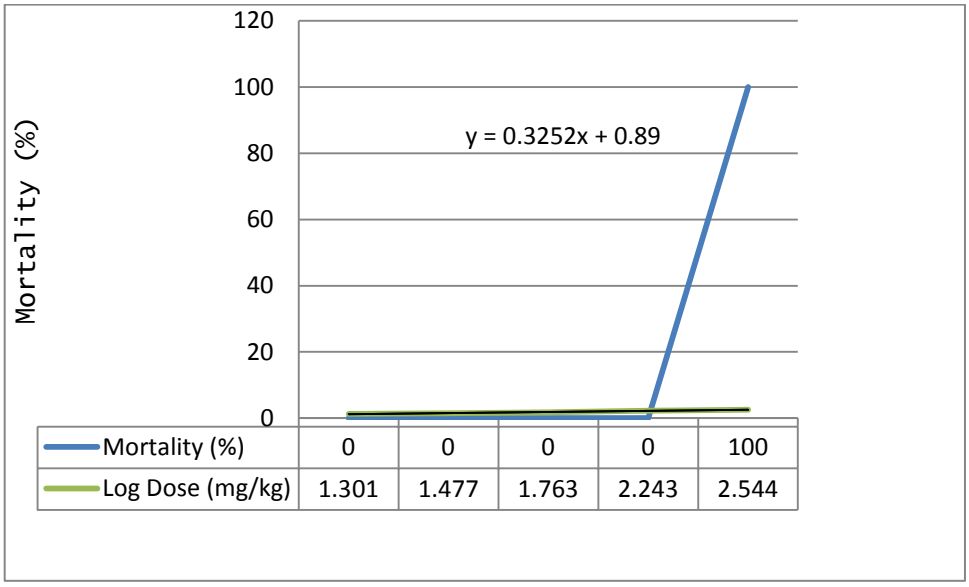

Figure 8: Toxicity of Ketamine Administered Intramuscularly to 40-day-old Chickens: Quantal Log-Dose Response Relationship.

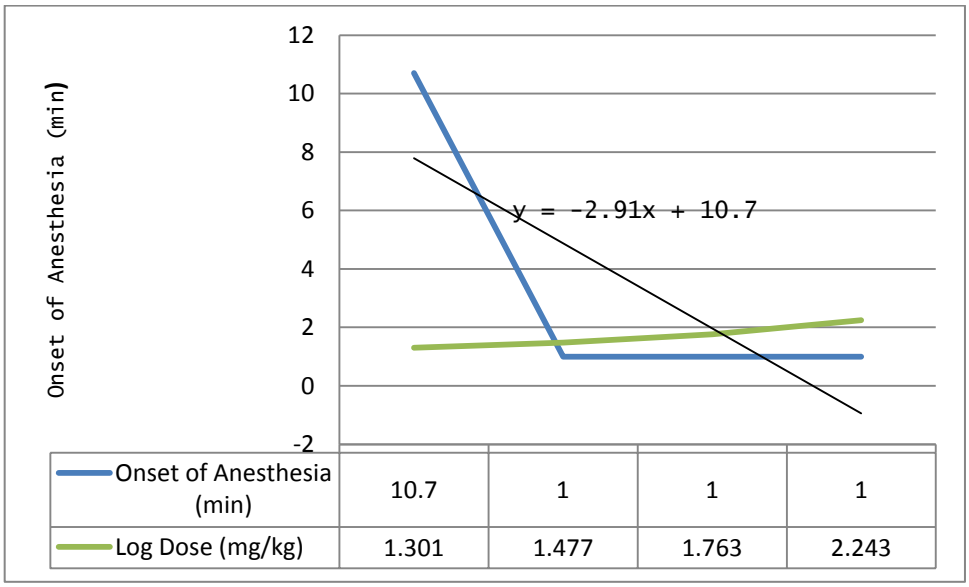

Figure 9: Onset of Ketamine –induced Anesthesia in 40-day-old Chicks.

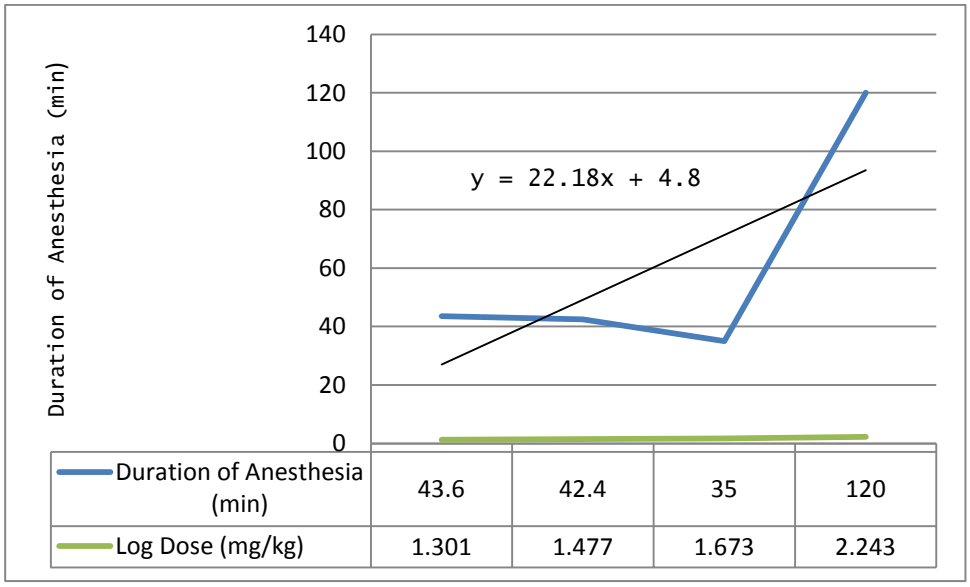

Figure 10: Duration of Anesthesia in 40-day-old Chickens Treated with Ketamine at Different Dose Levels.

CHAPTER FOUR

RESULTS

Chapter Four

Discussion

Ketamine is the most frequently used general anesthetic agent in birds and experimental animals (Ludders,1992 and Curro, 1998). It has good analgesic properties (Ronn *et al,* 2000 , Guilloun *etal,* 2003).

In this study doses ranging from 2.5 -10 mg/kg appeared to be well tolerated by young chicks compared with a dose level of 20 – 175 mg/kg in older birds. Apart from the group of birds treated at 20 mg/kg anesthesia was induced within 60 seconds in all trials. The anesthesia so produced was of a considerable duration ranging from 40-60 min in young birds to 35-120 min in older birds. Regardless of bird age, recovery from anesthesia was smooth and no untoward clinical reactions were recorded for up to 3 weeks by which time the experiments were terminated.

In past study , Ketamine is combined with diazepan and is found to be useful and produce fast and smooth induction of anesthesia, whilst dosage of ketamine alone produced a slow and smooth anesthesia.

In agreement with Ludders, Curro, Ronn and Guilloun in that ketamine can be used alone more effectively and safely and it will achieve good results when used.

The practical significance of testing ketamine in young chicks is that the domestic fowl *(Gallus domesticus*), as a species, is considered a unique experimental model in immunological research where surgical removal of the bursa of fabricius at an early stage results in depletion of the B-cell linkage and a permanent reduction in antibody production.

Schusser *et al* . (2013) described an advanced molecular technique leading to loss of antibody production and a block in B-cell development. Surgical bursectomy of newly hatched chicks, nevertheless, combined with sublethal

whole body x-irradiation, still remains an economically and a technically feasible technique to produce agammaglobulinemia. This surgical approach certainly requires an effective and a safe anesthetic agent for application in such small birds. Ketamine has been recommended for use in a wide range of avian species (Kittle, 1971; Paul-Murphy and Fialkowski, 2001 and Flecknell, 2009). Studies on the effects of this drug on small birds, however, are apparently lacking. Elowni and Hopkins (1981) used sodium pentobarbitoneintraperitoneal (I/P) injection to anesthetize 1-day-old chicks for bursectomy. The anesthetic, given at 40 mg/kg, diluted in Hanks Balanced Salt Solution was effective in inducing and maintaining anesthesia for at least 2 hours, a period sufficient for operation and the subsequent irradiation of the immobilized birds. Generally, the use of the I/P route for administration of anesthetics to birds is not a favored practice. This is probably because of the potential risk of puncturing the abdominal or caudal thoracic air sacs or perforation of an intestinal loop. Glatz *etal.* (2009) described an I/P injection technique of an anesthetic Tribromoethanol in birds without an adverse effect. The I/P injection of anesthetics was also found to be safe and effective in both CFLP and NIH mice enabling laparotomy and the subsequent transplantation of parasites into the duodenum (Elowni, 1980). In this respect, and regarding the small pectoral and thigh muscle mass of young birds, which renders I/M injection rather difficult, assessment of the intraperitoneal route for administration of anesthetics to young chicks may prove valuable in both veterinary practice and research. Ketamine may be reliably evaluating this uncommon technique in avian practice used for critically.

According to Sinn (1994), the drug is effective in various species of birds at dose of 5-75 mg/kg with a wide margin of safety in most of these species (Anon, 2001). In most instances, however, ketamine is used combinations

with other injectable agent such as xylazine , diazepam or midazolam to reduce or eliminate undesirable side effects if used alone (Maiti *et al,* 2006 , Durrani *et al,* 2014). The present study was performed to assess the performance of the ketamine as a general anesthetic when adminstered to domestic fowl. Assessment was made in terms of drug toxicity, the time for onset of the anesthesia and duration of the anesthesia.

Conclusion and Recommendation

Conclusion:

It is concluded that ketamine, when given intramuscularly can be used effectively and safely as a general anesthetic to domestic fowl and domestic fowl chicks. The results are of value in situations where resources are limited and it is not feasible to perform anesthesia with drug combinations or alternative methods such as inhalation anesthesia.

Recommendation:

We recommended that thus drug can be applied in veterinary practice dealing with poultry where the adult chickens is the subject or when young chicks are used in research particularly immunological research where surgery is the tool.

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