EFFECT OF CLONIDINE ON THIOPENTONE ANAESTHESIA IN RABBITS.

THESIS

Submitted to

The Faculty of Post-Graduate Studies
Sher-e-Kashmir University of Agricultural Sciences and Technology of Kashmir.

By

Nazir Ahmad
Registration No 97-V-28-M.

In partial fulfillment of requirements for the degree of

Master of Veterinary Sciences
(Veterinary Surgery & Radiology)

2001

DEDICATED

TO MY

BELOVED MOTHER

(May Allah, give peace to her soul)

Who cared for my education

SHER-E-KASHMIR

UNIVERSITY OF AGRICULTURAL SCIENCES AND TECHNOLOGY OF KASHMIR
Shalimar-191121,Srinagar,Kashmir

CERTIFICATE-I

This is to certify that the thesis entitled **"Effect of clonidine on thiopentone anaesthesia in rabbits"** submitted in partial fulfillment of the requirements for the degree of **Master of Veterinary Sciences (Veterinary Surgery & Radiology),** to the Faculty of Postgraduate Studies, Sher-e-Kashmir University of Agricultural Sciences & Technology of Kashmir is a record of bona fide research carried out by **Dr. Nazir Ahmad** (Regd No. 97/V/28/M) under my supervision and guidance. No part of the thesis has been submitted for any other degree or diploma.

It is further certified that such help or information received during the course of investigation have been duly acknowledged.

(Dr. Bashir Ahmad Moulvi)

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We, the members of the Advisory Committee of **Dr. Nazir Ahmad** (Registration No: 97-V-28-M), a candidate for the degree of **Master of Veterinary Science (Veterinary surgery & radiology),** have gone through the manuscript of the thesis entitled **"Effect of clonidine on thiopentone anaesthesia in rabbits"** and recommend that it may be submitted by the student in partial fulfillment of the requirements for the degree.

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CERTIFICATE-III

This is to certify that the thesis entitled **"Effect of clonidine on Thiopentone anaesthesia in rabbits"** submitted by **Dr. Nazir Ahmad,** to the faculty of Post – Graduate Studies, Shere-e-Kashmir University of Agricultural Sciences & Technology of Kashmir, in partial fulfillment of the requirements for the degree of **Master Of Veterinary Science(Veterinary Surgery and Radiology)** was examined and approved by the advisory committee and External Examiner (S) on 18 – 03 - 04

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ABSTRACT

Eighteen healthy NZL male rabbits were divided into three groups of six animals each. The animals of groups I and II were administered 2.5% thiopentone sodium intravenously and clonidine (16µg/kg Body weight) orally respectively. The animals of group III were premedicated with clonidine as in group II thirty minutes prior to the administration of thiopentone sodium as in group I.

The animals of group I showed anaesthesia and analgesia for 6-8 minutes at the anaesthetic dose of 32.04 µg/kg body weight and the recovery (to stand) was complete within 25-30 minutes. The only significant changes observed were decreased respiration rate, transitory increase in heart rate and decrease in total leuocyte count whereas the alterations in rectal temperature, haemoglobin, packed cell volume, differential leucocyte count, serum glucose, creatinine, sodium and potassium were not significant.

The animals of group II showed brief drowsiness for about 10 minutes and were awake, responsive and moved when provoked. Except the significant reduction inheart rate and respiration rate, all other physiological, haematocytological and biochemical changes were not significant.

The animals of group III showed anaesthesia of 9-13 minutes with excellent muscle relaxation at the thiopental dose of 25.89 mg / Kg body weight. The post anaesthetic analgesia and sedation were marked and recovery (to stand) began from 70-90 minutes. The only significant alterations included were decrease in respiration rate, leucopenia and hyperglycaemia throughout the study period.

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Place: Srinagar. (Nazir Ahmad)
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CONTENTS

INTRODUCTION

General anaesthesia in small animal became widely accepted with the discovery of barbiturates especially since 1934 with the introduction of thiopentone sodium by Ralph Waters at Wisconsin Hospital, Madison and was described and popularized by Dr. John Lundy at Mayo Clinic (Yates 1996). Thiopentone sodium is most widely used ultra short acting barbiturate anaesthetic in veterinary and medical anaesthesia due to its cost effectiveness, safety and easy availability. It is most popular, satisfactory, and clinically acceptable intravenous induction agent in the world both in veterinary (Mirakhur 1997) and medical anaesthesia (Yates 1996). It can be administered as a sole anaesthetic agent for operations especially which are not painful or when supplemented with analgesics and muscle relaxants (Lumb and Jones 1984 and Tripathi 1999). It has been used in different species of animals. It is anaesthetic of choice for dog and rabbit where in it is being used as sole anaesthetic agent.

In rabbit, thiopentone sodium is administered intravenously as a sole anaesthetic at the dose rate of 30-50 mg/kg body weights for 5-20 minute of anaesthesia (Booth 1988) and recovery is rapid (Lumb and Jones 1984). In dogs, thiopentone sodium is administered intravenously as induction agent at the dose rate of 6-8mg / kg body weight (Hall and Clarke 1983 and Lumb and Jones 1984) and as sole anaesthetic agent at the dose rate of 20-30 mg/kg body weight (Lumb and Jones 1984) for 10-20 minutes

of anaesthesia. The animal regains consciousness 60-90 minutes post induction (Pandey and Patel 1977). However there are various limitations to the use of thiopentone sodium as sole anaesthetic, which are: -

1. Its unsuitability for prolonged surgical procedures.

2. Its poor analgesic properties i.e., antanalgesic action in small doses and no analgesic action even in large doses (Reynolds and Prasad 1982).

3. Pain in the postoperative period is likely to induce restlessness and requires analgesia. (Tripathi 1999)

4. Its arrhythmogenic effect with tendency to cardiac dysrythmias (Hall and Clarke 1983)

5. Post anaesthetic shivering is common in all species of animals especially during cold weather (Hall and Clarke 1983), which is potential complication for surgical patients (Buggy et al.,1997)

6. Its potential hepatotoxic effects when used in large doses (Fedman and Scur 1979).

Different preanaesthetic agents have been tried for minimizing the different undesirable effects of anaesthetic agents and for relieving preoperative fear of patients so that anaesthesia can be induced smoothly without fright or struggling (Lumb and Jones 1984). Preanaesthetic agent supplements analgesic action of anaesthetic agents, potentiate them to reduce anaesthetic dose, to reduce secretions (Tripathi 1999) and to help in smooth recovery. Different preanasthetic agents viz., phenothiazine derivatives, opoids, benzodiazepines and alpha-2 adrenergic agonists have been used. Alpha-2 adrenergic agonists have found wide spread use in small animals due to their excellent combined sedative, analgesic and muscle relaxant properties and availability of antidotes. They have gained such a wide popularity that clinicians often overlook their potential and significant side effects (Singh 1997 and Mirakhur 1997).

The various alpha-2 adrenergic agonists which are being routinely used in veterinary practice are xylazine, medetomidine and detomidine whereas clonidine is mostly being used in medical anaesthesia. Clonidine, an alpha-2 adrenergic agonist (Pugh 1982) has many potential benefits in anaesthesia as preanaesthetic agent viz., anxiolysis, drying of secretions and produces preoperative sedation (Hoffman and Lefkowitz1996) better than diazepam (Mikawa et al., 1993). It has antinociceptive effect that is dose dependant (Solomon and Gebhart 1988, Segal et al., 1991 and Porchet et al., 1992). It also causes operative haemodynamics (Longnecker 1987) besides improving cardiovascular stability (Marshall and Longnecker 1996). Its antihypertensive potential is related to decreased sympathetic out flow from the brain (Maze and Tranquilli 1991). Clonidine has resulted in better and long postoperative analgesia (Carabine et al.1992) both in spinal (Liu et al. 1995) and general anaesthesia (Motsch et al., 1997) besides reducing the dose requirement of anaesthetics (Kuakinen and Pyykko 1979 and Ghignone et al., 1987, Eisenach et al., 1989, Richards et al., 1990 and Hayashi and Maze 1993). Clonidine has also reduced postanaesthetic shivering (Delaunay et al., 1991 and Buggy et al., 1997).

The present study was conducted on clonidine alone and as an adjunct to thiopentone sodium with the following objectives: -

1. To study the effect of clonidine on duration and quality of thiopentone anaesthesia in rabbits.

2. To study the effect of clonidine on various physiological functions in rabbits.

Review of literature

General anesthesia in small animals became widely accepted after the discovery of barbiturates particularly thiopentone sodium in 1934 (Lumb and Jones 1984). Thiopentone was originally synthesized by Tabern and Volwieler at Abbot Lab, USA in 1932. Its first recorded administration was made by Ralph Waters at Wisconsin Hospital, Madison in 1934.It was described and popularized by Dr John Lundy at the Mayo Clinic in the same year (Yate 1996). Thiopentone is an ultrashort acting barbiturate anaesthetic with a faint garlic smell and readily soluble in water. It is used as solution of different concentrations through intravenous route only. It has been used in different species of animals as an inducing agent but is anaesthetic of choice for dog and rabbit where in, it is used as a sole agent for general anaesthesia (Booth 1984). In dog and rabbit the dose rate for thiopentone anaesthesia is 20-30 mg/kg (Lumb and Jones 1984) and 30-50 mg/kg (Booth, 1984) body weight respectively for 5-20 minute of anaesthesia. After intravenous administration it quickly induces anaesthesia and hypnosis without excitement (Malik 1999). After administration it is distributed initially in highly vascular organs viz., brain and subsequently, the termination of its effects depends upon redistribution of drug from vessel rich tissues to lean body tissue like muscle, with return of consiousness. Slower redistribution then occurs to vessel poor tissues like fat (Yentis et al., 1995). Usual procedure is to administer 20-40 % of calculated dose moderately rapidly to produces hypnosis within 30-45 seconds and then injected slowly till effect. If the drug is injected slowly, stage of excitement may be encountered and if the drug in

higher dose is injected rapidly, profound anaesthesia may supervene with apnoea and hypotension with deleterious effect on circulatory system (Marshall and Longnecker 1996). Thiopentone reversibly depresses the activity of all excitable tissues. The central nervous system is particularly sensitive to the action of thiopentone and single anaesthetic induction dose has remarkably little effect on skeletal, cardiac or even smooth muscle (Dollery 1999). Thiopentone depresses the central nervous system in a dose dependant fashion, progressively producing sedation , sleep, unconsiousness, surgical anaesthesia , coma and ultimately fatal respiratory and cardio vascular depression (Hobbs et al.,1996). After central nervous system depression with thiopentone administration, pain perception and reactions are unaltered until consiousness is not lost. This is because analgesic effect of thiopentone on peripheral excitable tissue is weak and has no analgesic action even in large doses (Yentis et al., 1995), therefore thiopentone cannot be relied upon for painful operations. Due to this lack of analgesic effect thiopentone is regarded more as a hypnotic rather than an anaesthetic agent (Hall and Clarke 1983). Thiopentone sodium causes dose related direct myocardial depression (Carmichael and Hass 1998) lowering the force of heart contraction resulting in decreased cardiac output (Atkinson and Rushman 1977). This cardiovascular depression is also related to speed of injection and is exacerbated by hypovolaemia. The decreased cardiac output causes compensatory but transitory tachycardia. Heart rate increases significantly from 5-25 minutes after thiopentone administration with a maximum increase at 5 minutes after its administration in paediatric calves (Kandpal and Kumar 1998) and at 15 minutes after injection in horses (Tyagi et al., 1964) and diazepam premedicated peadiatric calves (Kandpal and Kumar 1998). In dogs, significant increase in heart rate has been documented at 5 minutes after

thiopentone administration which returned towards baseline value at 60 minutes after thiopentone administration (Rawlings and Kolata 1984 and Amarpal et al., 1999). Thiopentone causes dose related temporary depression of the respiratory center and reduced rate of respiration and apnoea is common after induction (Yentis et al, 1995). A deep breath or two or a yawn may preceed the depression. The depth of the breathing is related to external stimuli and a patient may breathe adequately once surgical manipulations provide a stimulus to respiration and within limits can off sets the respiratory depression (Marshall and Longnecker 1996). The laryngospasm and bronchospasm can be prevented by preanaesthetic atropine medication or by administration of succinyl choline immediately after thiopentone (Tripathi 1999). After thiopentone anaesthesia there is considerable decrease in respiration rate for a brief period in dogs (Amarpal et al., 1999) whereas in paediatric calves there is an initial transient but significant decrease in respiration rate at 5 minutes after aneasthesia (Kandpal and Kumar 1998) and from 5 to 25 minutes after anaesthesia in horse (Tyagi et al., 1964). Like other anaesthetics, thiopentone also alters body homeostatic mechanism particularly thermoregulation. BhaskarRao (1989) reported marked and progressive decline in rectal, oral and armpit temperature up to 45 minutes after administration of 1.25 % thiopentone at the dose rate of 20-30 mg/kg body weight in rabbits. A significant decrease in rectal temperature after thiopentone anaesthesia has been reported for 30 minutes in bovines (Amarpal and Kumar 1995), paediatric calves (Kandpal and Kumar 1998) and in dogs (Amarpal et al., 1999) however Singh & Dhablania (2000) did not observe any effect on rectal temperature after thiopentone–haloperidol anaesthesia in dogs. In bovines, thiopentone anaesthesia causes insignificant decrease in haemoglobin,

haematocrit, total erythrocyte count, total leucocyte count and differential leucocyte count (Amarpal and Kumar 1995 and Kandpal and Kumar 1998) but in dog and horse it causes significant decrease in total leucocyte count and insignificant changes in other blood parameters (Tyagi et al., 1964 and Usenik and CronKite 1965).The effect of thiopentone on various biochemical parameters are not of clinical significance. Thiopentone anaesthesia in bovines does not result in any significant change in urea nitrogen, creatinine, calcium, sodium, potassium and chloride levels in serum (Mirakhur et al., 1988; Amarpal and Kumar 1995 and Kandpal and Kumar 1998) however, mild hyperglycemia has been documented in dog (Booker et al., 1952), horses (Tyagi et al., 1964) and paediatric calves (Kandpal and Kumar 1998).Thiopentone anaesthesia reduces renal and hepatic blood flow due to reduced cardiac output however the functions of liver and kidney are depressed only transiently even with large doses of thiopentone (Fedman and Scur 1979 and Marshall and Longnecker 1996). The potential hepatotoxic effect of thiopentone does not make its use unsafe even with an already diseased liver as far as minimum doses are employed (Hall and Clarke, 1983 and Dollery 1999). Amarpal and Kumar (1995) recommended significantly less dose of thiopentone for hepatotoxic bovines, which was further reduced by pre anaesthetic medication with diazepam.Thiopentone causes brief and transient muscle relaxation at peak central nervous system level (Yentis et al., 1995), which occurs only at the onset of anaesthesia (Marshall and Longnecker 1996). This is because thiopentone does not effectively block the motor nerve impulses. The muscular relaxation is not well marked (Atkinson and Rushman, 1977) and can be enhanced with the proper preanaesthetic medication (Hall and Clarke 1983) as has been documented during acepromazine premedication in dogs

(Muir et al., 1975).Recovery following thiopentone anaesthesia is characterized by rapid awakening, usually stormy or even violent in nature like galloping in horse (Hall and Clarke 1983). Recovery (to standing) usually takes place within 15 minutes to 90 minutes in small animals including rabbit, dog and cat etc. In rabbit full recovery usually occurs within 15 minutes where as dog and paediatric calves regains consciousness 60-90 minutes post induction (Pandey and Patel 1977 and Kandpal and Kumar 1998).Post anaesthetic shivering after thiopentone anaesthesia is common both in man and animals especially during cold weather, as heat is generated to restore body temperature that has decreased during anaesthesia and surgery (Hall and Clarke 1983 and Marshall and Longnecker 1996). This post anaesthetic shivering is a potential complication for any surgical patient (Crossley 1992) and can be controlled by small doses of analgesic drugs (Hall and Clarke 1983 and Marshall and Longnecker 1996). In small doses, thiopentone acts as antanalgesic by lowering the pain threshold resulting in an increased sensitivity to pain i.e., hyperalgesia and have no analgesic action even in large doses (Reynold and Prasad 1982 and Carmichael and Haas 1998). Due to this poor analgesic property of thiopentone, pain in postoperative period after thiopentone anaesthesia is likely to induce restlessness and requires analgesia (Tripathi, 1999).The main complications associated with the use of thiopentone as anaesthetic are:-

a) Thiopentone does not prevent reflex response to painful stimuli and is therefore unsatisfactory by itself for painful operations.

b) Thiopentone causes respiratory depression which is relatively greater for a given degree of muscular relaxation and laryngospasm is usually common.

c) On repeated injections, recovery is prolonged as recovery depends on destruction of drug and not on redistribution of drugs (Laurence and Bennet, 1987).

However, most of the complications associated with thiopentone anaesthesia are minor and can be avoided or minimized by judicious use of thiopentone and addition of preanaesthetic medication. Also the analgesic drugs when used as preanaesthetic agents to thiopentone, affects the signs and stages of thiopentone anaesthesia favourably (Hall and Clarke 1983).

Preanaesthetic medication helps both the anaesthetist and the animal as it is valuable because it :-

i. Causes relief of anxiety and apprehension i.e., reduces stress preoperatively because of strange attendants, surroundings and surgical preparations (Walsch *et al*., 1987).

ii. Facilitates smooth induction, and the maintenance of anaesthesia becomes easier for the anaesthetist while at the same time renders the experience safer and more comfortable for patient (Hall and Clarke 1983).

iii. Supplements analgesic action of anaesthetic agent and potentiates them so that less anaesthetic agent is needed thus avoids the dangers of general anaesthesia (Tripathi 1999).

iv. Reduces pain, struggling and crying during recovery (Lumb and Jones 1984).

The most commonly employed classes of preanaesthetics are:-

a) Phenothiazine derivatives e.g., acepromazine, chlorpromazine etc.

b) Opoids e.g., morphine, mepridine etc.

c) Benzodiazepins e.g., diazepam etc.

d) Anticholinergic drugs e.g., atropine etc.

e) Alpha-2 adrenoreceptor agonists e.g., clonidine, xylazine, detomidine and medetomidine etc.

Various agents from all the above classes have been utilized as premedicants to thiopentone anaesthesia (Nigam and Peshin, 1993). But the alpha-2 agonists have found extremely widespread use in small animals and humans due to their excellent combined sedative analgesic and muscle relaxant effects and easy availability of specific antidotes. They have gained such wide popularity that clinicians often overlook their potential and significant side effects (Singh 1997). Beside alpha-2 agonists promote hemodynamic stability and keep homeostatic reflex intact and are antisialogogues. As far as clonidine is concerned, the available literature is mostly concerning humans and much less is available regarding the animals.

Clonidine has useful properties pertaining to anaesthesia. It is a partial agonist at alpha adrenoceptors both with in central nervous system and in the periphery but is more specific for alpha-2 adrenoceptors than for alpha-1 adrenoceptors. Its potential benefits include preoperative sedation, anxiolysis, dryness of scretions and analgesia (Hoffman and Lefkowitz 1996) and diminishes anaesthetic requirements and improves cardiovascular stability (Tripathi 1999). Effects of clonidine which appear from animal experiments, to be mediated by central alpha-2 adrenoceptor stimulation are hypotension,

bradycardia, enhanced baroreflex sensitivity, sedation, analgesia, hypothermia and change in motor activity and conditioned behaviour (Dollery, 1999).

Clonidine has been used as an adjunct to various local and general anaesthetics (Liu *et al*., 1995, Acalovschi *et al*.,1997 and Motsch *et al*.,1997) and produces sedation better than diazepam (Mikawa *et al*., 1993) with antinociceptive effect that is dose dependant (Solomon and Gebhart, 1988; Segal *et al*, 1991; Porchet *et al*., 1992 and Davies *et al*.,1997).

Clonidine has reduced the dose of inhalational and intravenous anaesthetics and analgesic drugs (Kaukinen and Pyykko, 1979; Bloor and Flacke, 1982; Flacke *et al*., 1987; Ghignone *et al*., 1987; Woodcock *et al*.,, 1988; Eisenach *et al*.,, 1989; Richards *et al*.,,1990; Hayashi and Maze 1993). Clonidine as a premedicant has significantly decreased the requirement for sufentanil at induction and isoflurane and propofol during anaesthetic maintenance (Liepert and Townsend, 1990 and Richards *et al*., 1990). As an adjunct, it has not only reduced dose of anaesthetics but also prolonged the duration of surgical anaesthesia (Bonnet *et al*., 1989; Ota *et al*., 1994 and Liu *et al*., 1995) with better and longer post operative analgesia (Carabine *et al*., 1992) both in spinal (Liu *et al*.,1995) and general anaesthesia (Motsch *et al*., 1997). Clonidine improved the perioperative (Ghignone *et al*., 1987 and Eisenach *et al*., 1989) and intraoperative haemodynamics (Longnecker 1987 and Liepert and Townsend 1990). Dekock *et al*., (1993 and 1997) have documented that the significant haemodynamic events have not to be feared from the intraoperative use of clonidine as an adjuvant because it provides dose control of haemodynamic changes associated with surgical stimulations and postoperative analgesia as demonstrated in propofol anaesthesia.

Clonidine has been reported effective in preventing the onset of postoperative shivering (Dull, 1993 and Horn *et al*.,1997). It even suppresses the established shivering

(Joris *et al*., 1993) whether given preoperatively (Flacke *et al*., 1987) during induction (Buggy *et al*., 1997) or immediately postoeratively (Delaunnay *et al*., 1991). Reduction in shivering is because clonidine lowers the body core temperature threshold for vasoconstriction and shivering (Delaunnay *et al*., 1993 and Nicolaou *et al*., 1997). Clonidine also decreases energy expenditure during recovery from anaesthesia (Quintin *et al*., 1991 and Takahashi *et al*.,1997). Clonidine is useful during postoperative pain; better than bupivacaine because of its analgesic effects (Carabine *et al*., 1992) and produces dose dependant postoperative analgesia without major side effects (Dekock *et al*., 1997). Clonidine has been usefully administered epidurally for the treatment of the pain in human cancer patients (Coombs *et al* 1984).

Clonidine causes fall in blood pressure accompanied by bradycardia and fall in cardiac out put (Davies *et al*., 1977 and Wilkinson and Raftery 1977). Clonidine has minor direct ventilatory effect (Bailey *et al*., 1991) but after over dose of clonidine, respiratory depression has been documented in humans, (Marruecos *et al*.,,1984, Narchi *et al*., 1992 and Takahashi *et al*., 1997) and rats (Gan and Abdul Sattar 1982) but not in ewes (Eisenach 1988).

Clonidine does neither impair renal functions (Hutler, et. al 1979 and Itskovitz 1980) nor does it alter normal renal hemodynamics as renal blood flow and glomerular filtration rate usually remain unchanged because of reduced renal vascular resistance (Onesti *et al*., 1971 and Itskovitz 1980). However there is modest retention of sodium and

chloride where as potassium excretion is unaffected (Dollery 1999 and Vickers *et al*., 1999). On the contrary, Liepert and Townsend (1990) have demonstrated that clonidine improves renal hemodynamics and postoperative renal functions in man.

Clonidine has been reported to cause mild transient increase in blood glucose (Warren *et al*.,1991 and Dollery 1999) but no significant change in serum creatinine levels (Liepert and Townsend, 1990).

Clonidine when administered alone does not impair either sensory or motor reflexes (Carabine *et al*., 1992). However, it occasionally causes hallucinations and dizziness in humans (Dollery, 1999). The ewes appear drowsy but awake, responsive and standing in their carts (Eisenach, 1988). Kimes *et al*.,(1990) reported that clonidine @ 200ug/kg. body weight reduces naloxone provoked withdrawl behaviour in animals with diarrhoea, wet-dog shakes and less abnormal posturing but increased grooming and jumping.

Clonidine can be safely used in patients with infection, sepsis, or systemic inflammation (Nishina *et al*., 1999) and does not produce any toxic effect of potential clinical relevance in various animal species (Dollery, 1999).

3

MATERIALS AND METHODS

The present study was conducted on eighteen apparently healthy New Zealand male rabbits aged 12-18 months in the weight range of 1.700-2.750 kg. The rabbits were procured from Angora Rabbit Farm, Sheep Husbandry Department, Wussan, Kashmir and were maintained under identical managemental conditions for a week prior to start of experiment .The animals were randomly divided into three groups of six animals each.

The animals of group I were administered 2.5% thiopentone sodium* intravenously till effect. The animals of group II were administered clonidine hydrochloride** orally at the dose rate of 16 µg/kg body weight (Paget and Barnes 1964)***. The animals of group III were administered clonidine hydrochloride as in group II followed half an hour later by thiopentone sodium as in group I.

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*-Thiosol (500mg)-Neon Laboratories Ltd. 28-Mahal Industrial Estate, Andheri (E) Mumbai.

** -Arkamin (100ug/tab)-Noble Medicure Pvt Ltd, Industrial Area Kakati, Belgaum (India). 591113.

*** -Dose for rabbit was calculated in the basis of human dose extrapoliated to rabbit by surface area ratio (Paget and Barbnes 1964.)

PREPARATION OF ANIMALS

Prior to experiment, the animals of all the groups were kept off feed and water overnight and physically examined to ensure the good state of health. Both the ear pinnae were shaved, scrubbed and dried. Before the start of the experiment, the body weight of each animal was recorded.

ADMINISTRATION OF DRUGS

1. Clonidine hydrochloride tablets were dissolved in 5ml of distilled water and the calculated dose of the drug was administered as gavage using 3ml plastic syringe.

2. Thiopentone sodium was administered intravenously through marginal ear veins using 22 No scalp vein set. About one half of the calculated dose was administered rapidly and after a pause of 30–45 seconds, the thiopentone was administered slowly till complete loss of tail pinch reflex.

RECORD OF PARAMETERS.

A.PHYSIOLOGICAL STUDIES.

The physiological parameters were recorded before the administration of clonidine hydrochloride or thiopentone and at 3, 8, 15, 30 and 60 minutes after the administration of clonidine hydrochloride or/and thiopentone sodium.

The various physiological parameters included were oral reflex, palpebral reflex, pinprick reflex and tail pinch reflex heart rate, respiration rate and rectal temperature.

In addition, amount of thiopentone utilized in group I and III, duration and extent of anaesthesia, postanaesthetic shivering, if any, and recovery time were recorded.

B.HAEMOCYTOLOGICAL AND BIOCHEMICAL STUDIES.

The marginal ear veins were raised by the application of xylene before the collection of blood. About 2.5–3.00 ml blood was collected before the administration of clonidine hydrochloride or thiopentone and at 5, 15, 30 and 60 minutes after the administration of clonidine hydrochloride or/and thiopentone sodium.

Out of the blood collected at any interval, about 0.5ml–1ml was collected in sterilized glass vials containing ethylene diamine tetracetic acid (EDTA) disodium salt at the rate of 1mg/ml of blood for the haemocytological investigations whereas remaining part was allowed to clot in 7ml sterilized dry glass tubes and was centrifuged. The serum obtained was used for estimation of various biochemical parameters.

HAEMOCYTOLOGICAL STUDIES.

The various haemocytological investigations included estimation of haemoglobin (Sahli's acid haematin method), packed cell volume (Microhaemoctocrit method), total leucocyte count and differential count as recommended by Ghai (1999). These investigations were completed within the three hours after the end of the experiment.

BIOCHEMICAL STUDIES.

The various biochemical parameters and their methods using diagnostic kits* included serum glucose by Glucose Oxidase Peroxidase mrthod (Trinder, 1969). serum creatinine by Alkaline Picrate method (Jaynes *et al*., 1971) and serum sodium and potassium by Ion – Selective method (Russell and Buckley,1988).

STATISCAL ANALYSIS OF DATA.

The data are presented as mean values ± typical error of mean. Computerised statiscal analysis was done using analysis of variance (ANOVA) and Duncans Multiple range tests. The significance was taken at 5 % ($P<0.05$) level.

* Supplied by Hospital Products Division, Nicholas Piramal India Ltd, Dadar (W), Mumbai- 400025.

PHYSIOLOGICAL STUDIES

For evaluating the physiological effect of oral clonidine and thiopentone sodium with or without oral premedication of clonidine, the various reflexes studied were oral (lip movements) reflex, palpebral reflex, pinprick reflex and tail pinch reflex (Table 1).

In animals of group II, there was no loss of any reflex during the study period, however, 10-15 minutes after the oral administration of clonidine, rabbits appeared drowsy for about 10 minutes but were awake, responsive and moved sluggishly when provoked.

In the animals of group I & III, there was immediate onset of anaesthesia with the administration of thiopentone and the various reflexes abolished in the following order i.e., oral reflex, palpebral reflex, pinprick reflex and tail pinch reflex and reappeared in reverse order during the recovery period. The observations made were as under: -

ORAL REFLEX: -

On the administration of thiopentone, the oral reflex was first reflex to be abolished in both the group I and III. It was regained lightly at 10.00 $\pm$ 2.00, moderately at 15.00 $\pm$ 3.00 and completely at 27.00 $\pm$ 4.00 minutes after the onset of anaesthesia in group I and at 26.00 $\pm$ 5.00, 34.00 $\pm$ 3.00 and 38.00 $\pm$ 4.00 minutes respectively in group III

PALPEBRAL REFLEX:-

The palpebral reflex also abolished during the thiopentone administration but after the loss of oral reflex in both group I and III. This reflex was regained lightly at 8.00 $\pm$ 1.00, moderately at 11.00 $\pm$ 2.00 and completely at 19.00 $\pm$ 2.00 minutes after the onset of anaesthesia in group I and at 18.00 $\pm$ 3.00, 27.00 $\pm$ 5.00 and at 35.00 $\pm$ 3.00 minutes respectively in group III.

PINPRICK REFLEX: -

Pinprick reflex abolished following loss of oral and palpebral reflexes. After the onset of anaesthesia, it was regained in group I, lightly at 7.00 ± 1.00, moderately at 9.00 ± 2.00 and completely at 14.00 ± 3.00 minutes and in group III at 14.00 ± 3.00, 16.00 ± 2.00 and 25.00 ± 3.00 minutes respectively.

TAIL PINCH REFLEX: -

Tail pinch reflex was last to abolish and marked the onset of anaesthesia in both group I and III. It regained lightly at 6.00 ± 1.00, moderately at 9.00 ± 1.00 and completely at 12.00 ± 3.00 minutes post anaesthesia in group I and at 11.00 ± 2.00, 14.00 ± 3.00 and 21.00 ± 4.00 minutes respectively in group III.

OTHER PHYSIOLOGICAL

OBSERVATIONS: -

HEART RATE: -

The heart rate (mean±SE) is given in table 2. It ranged from 232.33±5.38 to 268.00 ± 6.83, 202.33 ± 5.57 to 238.00 ± 8.16, and 225.67 ± 8.89 to 243.33 ± 6.23 per minute in animals of group I, II and III respectively. In the animals of group I, a significant ($P<0.05$) and abrupt increase in heart rate to a maximum of 268.00 ± 6.83 from (base value) 232.33 ± 5.38 was observed at 3 minute after onset of anaesthesia and declined thereafter insignificantly. The heart rate from 15 minutes post induction was statistically insignificant from the base value throughout the study period. The heart rate was near base value at the end of study period (235.33 ± 3.49). In animals of group II, clonidine administration decreased the heart rate. The heart rate was significantly ($P<0.05$) lower

than base value from 8 to 30 minutes after clonidine administration. At 60 minutes, the value (218.67 ± 7.77), though lower than base value, was not significantly different from it. In animals of group III the heart rate showed a slow and insignificant increase up to 8 minutes (243.33 ± 6.23) from base value (225.67 ± 8.89) and there after decreased slowly up to end of study period (229.67 ± 6.70) when the value was near normal.

Among the groups, the heart rate showed a significant ($P<0.05$) increase (268.00 ± 6.83) in group I when compared to that of group II (233.00 ± 8.48) and group III (238.00 ± 10.72) at 3 minutes. At 8, 15 and 30 minutes, after the onset of anaesthesia, the animals of group I and III showed a significant increase in heart rate as compared to the animals of group II at the same time. The mean heart rate was comparable at the end of study period in the animals of all groups. Among all the groups, the mean heart rate after drug administration, was highest in animals of group I through out the study period.

RESPIRATION RATE: -

The respiration rate (Mean ±SE) ranged from 35.83 ± 1.42 to 225.33 ± 13.65, 197.00 ± 2.62 to 214.67 ± 4.46 and 34.00 ± 3.09 to 193.67 ± 6.38 per minute in animals of group I, II and III respectively (Table 3).

In animals of group I, the respiratory rate decreased significantly ($P<0.05$) at 3 minute after onset of anaesthesia, thereafter showed an insignificant increasing trend throughout the study period. However the respiration rate was significantly ($P<0.05$) lower up to 30 minute (149.33 ± 29.33). The value at 60 minutes (198.33 ± 23.69) was insignificantly lower than the base value (225.33 ± 13.65).

In animals of group II, the mean respiratory rate recorded was lower than base value throughout the study period, however, the decrease was significant ($P<0.05$) only at 8 and 15 minutes after drug administration. The maximum decrease was observed at 8 minutes (197.00 $\pm$ 2.62) thereafter showed an insignificant increase up to the end of the study period when the value was near normal (206.33 $\pm$ 4.39).

In animals of group III, the respiration rate remained significantly ($P<0.05$) lower throughout the study period from the base value (193.67 $\pm$ 6.38). However the maximum decrease was recorded at 3 minute (34.00 $\pm$ 3.09) after the onset of anaesthesia. Thereafter, the value increased insignificantly to a maximum of 86.00 $\pm$ 24.94 at the end of study period.

The respiratory rate in group I showed a significant ($p<0.05$) decrease in respiratory rate at 3 minute and continued up to 15 minutes when compared to that of group II, where as the respiratory rate in group III showed a significant ($p<0.05$) decrease from 8 minutes up to the end of study period when compared to that of group I and throughout the study period when compared to that of group II.

RECTAL TEMPERATURE: -

The rectal temperature (Mean ± SE) in various groups of animals ranged from 102.13 ± 0.57 to 103.30 ± 0.25^0 F. In all the three groups, no significant change but slight fluctuations were observed within and between the groups (Table 4).

ADDITIONAL OBSERVATIONS: -

Laryngospasm was observed during induction in four out of six rabbits in group I. Two rabbits showed shivering and in one rabbit; only trembling of limbs was seen. Whole body jerky movements were noticed in two rabbits ten minutes after induction. The animals of group III did not show these signs. However, marked postanaesthetic sedation with drowsiness (fig 1)was recorded in rabbits of group III up to 45-65 minutes. The animals of group I began to move from 25-30 minutes post anaesthesia with ataxia and dragging of hind legs. The normal movement of the animal was restored near the end of study period. One rabbit urinated 58 minutes after the induction.

The animals of group III, began to move from 45-60 minutes post induction. The animals were falling on either side and dragging their hind limbs. At 70-90 minutes, the rabbits started to stand on hind limbs but could not maintain the balance. Normal movement was, however, observed after two hours. Protrusion of penis (fig 2)was observed in all the six rabbits of group III. The protrusion of penis was marked at 4.00 ± 2.00, moderate at 9.00 ± 3.00 and slight (appearance of glans only) at 12.00 ± 2.00 minutes post induction. Relaxation of anal sphincter was also observed in this group while recording the rectal temperature. The relaxation of sphincter was marked at 3 minutes, moderate at 30 minutes and slight at the end of the study period.

Dosage of thiopentone sodium.

The dose of thiopentone sodium administered intravenously for general anaesthesia (to effect) was recorded in rabbits of both group I and III (Table 5). The average dose required in animals of group I was found to be 32.04 mg/kg body weight where as in clonidine premedicated rabbits (Group III), the average dose found to be 25.89mg/kg body weight.

HAEMOCYTOLOGICAL OBSERVATIONS: -

HAEMOGLOBIN: -

Mean ± SE of haemoglobin (gm %) in different groups of rabbits ranged from 12.10±0.85 to 14.00±0.79 gm% (Table 6). Animals of all groups showed an insignificant but gradual decrease in haemoglobin percentage up to the end of study period. There was also no significant change in haemoglobin percentage among the groups during the study period.

PACKED CELL VALUE: - The value of packed cell volume % (Mean± SE) ranged from 41.33 ± 2.11 to 37.83 ± 1.30, 36.67 ± 1.50 to 32.67 ± 1.45, and 36.00 ± 1.00 to 35.33 ± 1.31 % in animals of group I, II and III respectively (Table 7).

The animals of all the groups showed insignificantly lower values through out the study period from their respective base values however the maximum decrease was observed as 37.83 ± 1.30, 32.67 ± 1.45, and 35.33 ± 1.31 % at 15 minutes. Thereafter, the

value increased to 40.00 ± 1.44, 34.00 ± 1.24 and 35.50 ± 0.92 % at the end of the study period in group I, II, III respectively

TOTAL LEUCOCYTE COUNT:-

The total leukocyte count (Mean ± SE) is depicted in Table 8. The total leucocyte count (TLC) ranged from 6.95 ± 0.29 to 8.95 ± 0.37, 8.15 ± 0.69 to 8.87 ± 0.88 and 7.12 ± 0.37 to 9.40 ± 0.75 thousand/cmm in group I, II and III respectively

In group II, the animals showed slow and insignificant decrease to a minimum of 8.15 ± 0.69 thousand /cmm at 15 minute from base value of 8.31 ± 1.00 and there after increased insignificantly to 8.72 ± 0.80 thousand /cmm, slightly higher than base value at the end of study period.

In the animals of group I and III, TLC decreased significantly ($P<0.05$) 5 minutes after the induction of anaesthesia. The count continued to decrease slowly up to 15 minutes and thereafter, the TLC started to increase but was still significantly ($P<0.05$) lower than their base values at the end of the study period.

DIFFERENTIAL LEUCOCYTE COUNT:-

LYMPHOCYTES: -

The lymphocyte (Mean±SE) % values are given in table 9. It ranged from 57.17 ± 1.42 to 58.00 ± 1.71, 58.12 ± 2.18 to 60.17 ± 2.52 and 54.83 ± 1.62 to 56.33 ± 1.86 % in group I, II and III respectively. There was no significant change within or among the groups .The lymphocytes count fluctuated within the normal range through out the study period.

NEUTROPHIL: -

The neutrophil (Mean±SE) % values are given in table 10. It ranged from 38.17 ± 1.70 to 39.50 ± 2.05, 35.50 ± 2.03 to 38.00 ± 1.69 and 39.17 ± 2.07 to 40.83 ± 1.78 % in group I, II and III respectively. There was no significant change within or among the groups and the neutrophil count fluctuated within the normal range through out the study period.

SERUM BIOCHEMICAL ANALYSIS: -

GLUCOSE: - The glucose values (Mean ±SE) of the various groups of the animals are given in Table 11. It ranged from 127.83 ± 8.28 to 138.00 ± 9.81, 120.00 ± 5.13 to 132.83 ± 7.06 and 123.50 ± 4.12 to 172.67 ± 6.91 mg/100ml in group I, II and III respectively. The animals of group I and II showed insignificantly higher values throughout the study period from their base values. In the animals of group III, the glucose value increased significantly ($P < 0.05$) from 5 minutes after injection of thiopentone. The values continued to increase throughout the study period and at 30-60 minutes post injection, the glucose level was significantly ($P< 0.05$) higher than that at 5 minutes post injection.

CREATININE: - The serum creatinine values (Mean ± SE) are presented in Table 12. The values ranged from 1.04 ± 0.19 to 1.24 ± 0.05, 1.23 ± 0.07 to 1.26 ± 0.04, and 1.30 ± 0.03 to 1.33 ± 0.84mg/100ml in group I, II and III respectively. The creatinine values did not show any significant change within or among the groups. A slight decrease at 5

minutes after the drug administration was observed in the group I and II whereas in group III, slight increase was observed at 30 minutes after the onset of the anaesthesia.

SODIUM: - The serum sodium values (Mean ± SE) ranged from 133.33 ± 6.13 to 140.33 ± 1.43, 142.33 ± 3.02 to 154.67 ± 7.21, and 137.50 ± 1.06 to 140.50 ± 1.23 mEq/litre in group I, II and III respectively (Table 13). The animals of all the groups showed insignificantly higher serum sodium values throughout the study period from their respective base values and the maximum increase was observed at 15,5 and 15 minutes in animals of group I, II,and III respectively. While comparing groups, group II showed significantly ($P < 0.05$) higher values at 5 minutes than other two groups.

POTASSIUM: - The serum potassium level (Mean ± SE) are shown in Table 14. The values ranged from 4.03 ± 0.17 to 4.23 ± 0.22, 4.50 ± 0.24 to 4.77 ± 0.28 and 4.13 ± 0.12 to 4.25 ± 0.15 mEq/litre in the group I, II and III respectively. The serum potassium values did not show any significant change in any of the group however the potassium level increased slightly to 4.77 ± 0.28 mEq/litre from the base value 4.68 ± 0.29 mEq/litre at 5 minutes in group II and decreased thereafter to a minimum of 4.50 ± 0.24 mEq/litre at the end of the study period. Whereas the trend was reverse in group I and III. While comparing groups, the animals of group II showed significantly ($P<0.05$) higher serum potassium values at 5 and 30 minutes after the administration of the drug than group I and III.

DISCUSSION

The oral administration of clonidine and intravenous administration of thiopentone sodium with or without oral premedication of clonidine was evaluated in rabbits

The oral administration of clonidine (16µg/kg bodyweight) neither produced analgesia nor impared the motor responses. However, 10-15 minutes after the administration of clonidine, rabbits appeared drowsy for about 10 minutes but were awake,responsive and moved sluggishly when provoked. Similar mild sedative effects with clonidine have been reported in ewes (Eisenach. 1988) and man (Carabine *et al.,* 1992). Mikawa *et al.,* (1993) reported that the sedation produced by clonidine was better than diazepam in man. Another alpha-2 agonist medetomidine has also been reported to produce only sedation in rabbits (Sharma *et al.,* 1999) and goats (Chitalee *et al.,* 1999).

The thiopentone sodium (2.5%) produced anaesthesia of 6-8 minutes at the average dose of 32.04 / kg body weight. Booth (1984) has reported 5-20 minutes duration of anaesthesia at the dose rate of 30-50 mg / kg body weight in rabbits with recovery time of 15 minutes (Murdock, 1969 and wood, 1978). Complete recovery (to stand) began from 25-30 minutes after onset of anaesthesia and normal movement was restored within 55.00± 5.00 minutes. Laryngospasm at the time of induction and post anaesthetic shivering observed in the present study is common with thiopentone anaesthesia in all species of animals (Hall and Clarke 1983). The post anaesthetic shivering is very distressing for patients (Brownbridge 1986) and is a potential complication for surgical patients (Crossley, 1992 and Buggy *et al.,* 1997). This shivering is due to reduction of shivering threshold by anaesthetic agents (Jensen, 1980). It has been reported that shivering might increase the risk of myocardial infarction (Dull, 1993), the gravity of which becomes more severe in animals anaesthetized with thiopentone because of its depressive effect on myocardium. The premedication with oral clonidine to thiopentone anaesthesia has increased the duration of anaesthesia, enhanced the analgesia

with excellent muscle relaxation however the recovery was smooth but prolonged and without shivering. Besides,it reduced the dose of thiopentone sodium. Clonidine premedication increased the duration of anaesthesia from 6.00 ± 1.00 minutes to 11.00 ± 2.00 minutes and the analgesia (loss of pinprick reflex) from 7.00 ± 1.00 to 14.00 ± 3.00 minutes. Kumar and Singh (1995) has reported that in dog, the pareanthetic medication with neuroleptanalgesic agents to thiopentone has increased the duration of surgical anaesthesia , prolonged the recovery time and reduced the dose of thiopentone. Similar finding with increased duration of surgical anaesthesia and better and longer postoperative analgesia in man has also been reported with clonidine (Bonnet *et al.,* 1990; Carabine *et al.,* 1992; Ota *et al.,* 1994; Liu *et al.,* 1995 and Motsch *et al.,* 1997). The increase in the duration of anaesthesia is because the clonidine potentiates the effect of local and general anaesthetics(Richards, *et al.,* 1990;Liu *et al.,* 1995;Acalovschi *et al.,* 1997;Dekock *et al.,* 1997 and Mostsch *et al.,* 1997)This increase in the durationof analgesia is probably due to antinociceptive effect of clonidine (Solomon and Gebhart,1988; Segal *et al.,* 1991 and porchet *et al.,* 1992) and is desirable in surgical patients as the pain in the post operative period after thiopentone anaesthesia is likely to cause restlessness because of antanalgesic effect of thiopentone (Tripathi,1999). Clonidine-thiopentone combination result in complete muscle relaxation exhibited by the protrusion of penis and relaxation of anal sphincter and is probably due to the potentiating effect of clonidine on thiopentone. No protrusion of penis or relaxation of anal sphincter wae observed after thiopentone administration ,because muscle relaxation was not well marked as thiopentone cause brief skeletal muscle relaxation at peak central nervous effect (Atkinson and Rushman,1977; Yentis *et al.,* 1995 and Tripathi,1999). Similar effects have been reported after haloperidol-thiopentone combination in dogs (Sing and Dhablania, 2000) and with medetomidine (alpha-2 agonist)-ketamine combination in rabbits (Sharma *et al.,* 1999) and goats (Hugar *et al.,* 2000).

Clonidine premedication to thiopentone anaesthesia has resulted in smooth but prolonged recovery without any untoward effect like shivering. Prolonged recovery after clonidine premedication has also been reported in humans (Mikawa *et al.,* 1993) and has been attributed to the sedative effect of clonidine (Richards *et al.,* 1990).

Clonidine premedication inhibited or prevented the post anaesthetic shivering. Similar finding have been reported in humans (Flacke *et al.,* 1987; Quintin *et al.,* 1991; Dull 1993; Joris *et al.,* 1993 and Taittonen *et al.,* 1997). This inhibition of shivering is because clonodine decreases the body core temperature threshold for vasoconstriction and shivering (Nicolaou *et al.,* 1997) and decrease the metabolic requirements of patient (Rodriquez *et al.,* 1983). This action has been utilized during recovery in human anaesthesia.

No laryngospasm was observed in clonidine-thiopentone anaesthesia. Clonidine premedication has also probably prevented the laryngospasm as has been reported by other preanaesthetic medication in thiopentone anaesthesia (Tripathi 1999).

The average anaesthetic dose of thiopentone sodium was reduced by 19.19% (from 32.04 to 25.89 mg / kg body weight). Similar reports have been found where clonidines have been used with either intravenous (Orko *et al.,* 1987 Richard *et al.,* 1990) or inhalant (Ghignone *et al.,* 1987; Racle *et al.,* 1987 and Ghignone *et al.,* 1988) anaesthetic agents. Likewise, the thiopentone requirement has also been effectively reduced by various preanaesthetic agents like atropine (Klide *et al.,* 1974), diazepam (Amarpal and Kumar, 1995 and Kandpal and Kumar, 1998), haloperidol (Singh and Dhablania, 2000), promazine, xylazine, mepridine and detomidine etc (Nigma and Peshin, 1993).

HEART RATE:-

A significant but transitory increase in heart rate was observed immediately after the thiopentone anaesthesia in rabbits. The similar effects have been reported to occur with thiopentone in horses (Tyagi *et al.,* 1964), bovines (Amarpal and Kumar, 1995), paediatric calves (kandpal and Kumar, 1998) and dogs (Amarpal *et al.,* 1999). This increase in heart rate has been attributed to compensate the decreased cardiac out put as

aresuly of direct myocardial depression of thiopentone (Yentis *et al.,* 1995). However this tachycardia is of no clinical importance in normal hearts in fit patients receiving moderate doses of the drug (Atkinson and Rushman, 1977). The clonidine administration in rabbits result in significant fall in heart rate from 8 to 30 minutes and this effect of reducing heart rate has been reported in ewes (Eisenach, 1988), dogs (Ghignone *et al.*, 1988) and humans (Davies *et al.,* 1977; Wilkinson and Raftery 1977; Dekock *et al.*, 1993; Liu *et al.,* 1995; Motsch *et al.,* 1997 and Takahashi *et al.,* 1997).This depressive effect has also been reported with other alpha-2 agonists like medetomidine in rabbits (Sharma *et al.,* 1999), detomidine in calves (Kmar and Muralikrishna, 1998) and xylazine in dogs (Peshin *et al.,*1980) and horse (Hall and Clarke, 1983) and both xylazine and detomidine in buffaloes (Tiwari and Kumar, 1998).

The cardiac depression after clonidine administration has been attributed to decreased symphathetic outflow from central nervous system (Antonaccio *et al.,* 1973), vagal activation due to central nervous activation of alpha-2 adrenoceptors, potential prejunction alpja-2 inhibition at cardiac pacemaker tissue (Raekallio, 1992) and involvement of baroreceptor reflex induced by alpha-2 agonists.

However, after thiopentone anaesthesia in clonidine premedicated rabbits, neither bradycardia nor tachycardia was observed and heart rate ranges in between that recorded in the animals of group I and II. This reduction in tachycardia after thiopentone administration is beneficial in patients at risk of developing inadequate cardiac output or myocardial ischaemia (Roizen, 1988). This improvement in hemodynamic stability with the use of clonidine as preanaesthetic medicant has also been documented in dogs (Ghignone *et al.,* 1988) and humans (Ghignone *et al.,* 1987; Eisenach *et al.,* 1989; Liepert and Townsend, 1993 and Dekock *et al.,* 1993).

RESPIRATION RATE:-

Thiopentone , Clonidine and their combination produced the depression of respiration. After thiopentone administration, the respiratory decreased abruptly (from 225.33 ± 13.65 to 35.83 ± 1.42/min). This decrease was transient as it increased (to 73.17 ± 14.02 / min) at 8 minutes. This could be due to the depression of the medullary respiratory center by thiopentone (Yentis *et al.*, 1955). However, this respiratory depression by normal doses of thiopetone is not a clinical problem in fit patients (Dollery,1955). Similar findings have been reported after thiopentone anaesthesia in horse (Tyagi *et al.*, 1964),goats(Singh and Kumar, 1988) and paediatric calves (Kandpa and Kumar, 1998).

On oral administration of clonidine, a slight respiratory depression was observed . the respiratory rate decreased to a minimum of 197.00± 2.62 from 214.67± 4.46 At 8 minutes and was within the normal limits through out the study period. This mild respiratory depression hae been also reported in humans (Motsch *et al.*, 1997 and Takashi *et al.*, 1997) and is attributed to the decreased slope of ventilatory response to carbon dioxide (Narchi *et al.*, 1992).Similar decrease had been reported with other alpha-2 agonists like medetomidine in rabbits (Sarma *et al.*, 1999) and dogs (Amarpal *et al.*, 1999) detomidine in calves (Kumar and MuraliKrishna1998) and xylazine in dogs (Peshin *et al.*, 1980), buffaloes(Kumar *et al.*, 1991) and bovine calves (Choudhary *et al.*, 1998).

Comparatively, a greater and prolonged decrease in respiratory rate was observed in clonidine premedicated rabbits after thiopentone anaesthesia and could be attributed to the combined effect of these drugs, however, the minimum rate of respiration during the study period viz., 34.00 ± 3.09 / min (at 3 minutes) was still higher than the minimum desirable respiration rate in rabbit anaesthesia i.e., 18-24 / min (Lumb and Jones.1984).

TEMPERATURE :-

No significant change in rectal temperature was observed after the oral administration of clonidine or after intravenous administration of thiopentone with or without clonidine premedication in rabbits. Similar observations have been reported after thiopentone administration in dogs (Singh and Dhablania, 2000).

However, the slight fall in rectal temperature after the administration of clonidine with or without thiopentone in the animals of group II and III, has also been observed with other alpha-2 agonists like medetomidine in goats (Amarpal *et al.,* 1998), detomidine in buffaloes (Peshin and Kumar. 1979) and calves (Kumar and MuraliKrishna 1998) and xylazine in mares (Skarda and Muir. 1994) and also with diazepam with or without thiopentone in bovines (Amarpal and Kumar. 1995) and paediatric calves (Kandpal and Kumar 1998). This slight fall in rectal temperature may be due to decreased basal metabolic rate and reduced muscular activity as a result of sedative effect of clonidine.

HAEMATOLOGICAL STUDIES:-

All the anaesthetic and tranquillizers appear to cause some blood change, however ,variable results have been reported during anaesthesia. A reduction in packed cell volume and haemoglobin concentration may been due in part to dilation of spleen during anaesthesia and consequent haemodilution caused by water shift. Bolbol (1979) regarded the decline in total erythrocyte count, haemoglobin and packed cell volume to an erythrocyte storage in the spleen as a result of pooling of blood rather than the dilution of blood due to shift of fluid from interstitial space. Studing thiopentone anaesthesia with or without diazepam, no decrease in haemoglobin concentration and packed cell volume was reported in horses (Tyagi *et al.,* 1964), dogs(Usenik and Cronkite.1965), goats(Kinge *et al.,* 1985), bovines (Amarpal and Kumar. 1995) and paediatriccalves(Kandpal and Kumar. 1998).similar changes have been reported after administration of alpha-2 agonists like xylazine in cattle(Kumar and Singh.1976) and dogs(Peshin *et al.,* 1980) and xylazine and detomidine in goats (Kumar *et al.,* 1997).

In the present study, a slight decrease in packed cell volume and haemoglobin percentage within the normal physiological limits was observed after the administration of clonodine or /and thiopentone.

After clonidine administration , no significant change was observed in total leucocyte count. Administration of thiopentone with or without clonidine premedication resulted in a significant decrease in total leucocyte count throughout the study period. The leucopenia observed after thiopentone administration was also observed in horses (Tyagi *et al.,* 1964) and dogs(Usenik and Cronkite. 1965)

An inconsistent and insignificant change in differential leucocyte count within the normal physiological limits was observed in the animals of all groups. Similar observations were reported after thiopentone anaesthesia in dogs (Usenik and Cronkite. 1965) and bovines (Amarpal and Kumar. 1994)

BIOCHEMICAL STUDIES :-

In the present study ,an increase in the serum glucose was observed in the animals of all groups. The increase was mild in rabbits after clonidone or thiopentone administration whereas, in clonidine premedicated rabbits, the hyperglycaemia was significant through out the study period after the thiopentone anaesthesia.

Hyperglycaemia has been reported after thiopentone administration in horses (Tyagi *et al.,* 1964), humans (Atkinson and Rushman. 1997 and paediatric calves (Kandpal and Kumar 1998). Hyperglycaemia has also been reported after clonidine(Dollery. 1999) and other alpha-2 agonists like medetomidine in goats(Chitale

et al., 1999), xylazine in horses (Kumar and Singh . 1978) and dogs (Peshin *et al.,* 1980) and xylazine and detomidine in goats(Kumar *et al.,* 1997). Elevated blood sugar level has been correlated with the rise in cortisollevel during stress. Blood sugar level rises slowly with the rise in cortisol level and fluctuates as the cortisol level decreases (Steyn. 1969). A mild hyperglycaemia occurs during anaesthesia due to impairment of patient's ability to handle a glucose load. However, hyperglycaemia after thiopentone may be normal response to stress rather than the effect of drug on glucose metabolism (Dollery.1999) whereas clonidine is reported to suppress the stress hormone release and increases the serum glucose due to inhibition of insulin release (Metz *et al.,* 1978 and Joffe *et al.,* 1986).

The concentration of creatinine in blood or urine is influenced by the severe renal damage (Kelly.1984). In the present investigation, serum creatinine lele showed only fluctuation within the normal physiological limits throughout the study period. This is in agreement with the findings of Amarpal and Kumar (1995) and indicates little or no effect of these drugs on kidney functions (Dollery. 1999). Renel diseases are not contraindications to thiopentone (Atkinson and Rushman. 1977) or clonidine (Laurence and Bennet, 1987). Premedication of Clonidine to sufentanil anaesthesia has been reported to improve renel haemodynamics with no elevation in serum creatinine concentration (Itskovitz. 1980 and Liepert and Townsend.1990).

The electrolytes in body are not simply inert inorganic salts but fulfill a vital role in life processes. The transmembrane movement of electrolytes is responsible for the electrochemical events that result in nerve conduction and muscular contraction including center element of cardiovascular system. Clonidine is reported to reduce the sodium and chloride excretion whereas potassium excretion is unaffected (Vickers *et al.,* 1999). The thiopentone causes a small but persistent fall in potassium concentration in blood (Hall and Clarke, 1983). It is further supported by the observations of Adriani (1962) that changes in sodium concentrations are not due primarily to the effect of anaesthetic drugs itself but result secondarily from the aberrations induced by anaesthetic state. Salt

retention, changes in tubular functions, impairment of water absorption and changes in permeability of endothelial membranes are the factors, which could influence electrolyte change.

In present investigation, insignificant changes in sodium and potassium within the normal physiological limits were observed in animals of all groups.these insignificant changes in sodium and potassium indicated that the homeostasis was largely maintained after the administration of clonidine, thiopentone or their combination. Similar findings were reported after thiopentone anaesthesia with or without diazepam in bovines (Amarpaland Kumar.1995) and calves (Mirakhur *et al.*,1988 and Kandpal and Kumar.1998) and also after the administarion of alpha – 2 agonists like xylazine in dogs (Peshin *et al.*, 1980).

The changes in the level of biochemical parameters like creatinine, sodium and potassium were insignificant indicating that kidney functions and electrolyte balance remained unaffected.

SUMMARY AND CONCLUSION

Eighteen healthy male NZL rabbits aged 12 – 18 months weighing 1.7 – 2.750 Kgs were divided into three groups of six animals each. The animals were kept off feed and water over night prior to the administration of drugs. The animals of groups I and II were administered with 2.5% thiopentone sodium intravenously till effect and clonidine orally (@ 16 µg / Kg body weight), respectively, where as the animals of group III were administered with clonidine as in group II thirty minutes prior to thiopentone administration as in group I.

In animals of all groups oral, palpebral, pinprick and tail pinch reflexes, heart rate, respiration rate and rectal temperature were recorded immediately before and 3,8,15,30 and 60 minutes after clonidine or / and thiopentone administration.

The blood samples of 2.5 – 3.00 ml were collected immediately before and 5,15,30 and 60 minutes after clonidine or / and thiopentone administration. 0.5 – 1.00 ml blood was transferred into sterilized glass vials containing EDTA for haemoglobin, packed cell volume, total and differential leucocyte counts. Remaining 2.00 ml blood sample was transferred into plain glass tube for collection of serum for estimation of glucose, creatinine, sodium and potassium.

Besides time of complete recovery (restoration of normal movements), protrusion of penis, relaxation of anal sphincter, shivering and other side effects, if any, were also studied.

The animals of group I showed laryngospasm at induction, 5-7 minute anaesthesia as judged by tail pinch reflex, post anaesthetic shivering and quick recovery with restoration of normal movement near the end of study period. The animals of group II showed mild sedation with drowsiness without any loss of reflex. The animals were awake, responsive and moved sluggishly when provoked. The animals of group III

showed prolonged analgesia and sedation with 9-13 minute anaesthesia with excellent muscle relaxation. The recovery was prolonged without shivering and normal movement was restored after two hours. The anaesthetic dose of thiopentone sodium was reduced by 19.9%.

The animals of groups I & II showed tachycardia (Transient) and bradycardia, respectively but no significant change in heart rate was observed in group III. The respiration rate was low throughout the study period in all groups. The decrease was significant upto 30 minutes in group I, from 8 to 15 minutes in group II and through out the study period in group III. Rectal temperature showed no significant change throughout the study period in any group.

No significant change was observed in haemoglobin, packed cell volume and different leucocyte count in animals of any group. The leucocyte was significant after thethiopentone administration throughout the study period in animals of groups I & III where as in animals of group II no significant change in total leucocyte count was observed, Hyperglycaemia was observed in animals of all groups throughout the study period but was significant only in animals of group III. The serum creatinine, sodium and potassium did not show any significant change in animals of any group.

From the present study, following conclusions were drawn:-

a. Clonidine in rabbits produced a brief drowsiness without any detectable analgesia,
b. Clonidine premedication to the thiopentone anaesthesia in rabbits resulted in :-
    1. Prolonged anaesthesia and analgesia with excellent muscle relaxation.

2. Marked Post anaesthetic sedation.
3. Prolonged but smooth recovery without shivering.
4. Reduced the anaesthetic dose of thiopentone by 19.19% in rabbits.
5. Improved the cardiovascular stability but prolonged and increased the
6. respiratory depression.

7

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