TILETAMINE-ZOLAZEPAM ANAESTHESIA WITH XYLAZINE PREMEDICATION AND REVERSAL WITH AMINOPHYLLINE IN DOGS

By

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THESIS

Submitted in partial fulfilment of the requirement for the degree

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Faculty of Veterinary and Animal Sciences
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DECLARATION

I hereby declare that this thesis entitled **TILETAMINE-ZOLAZEPAM ANAESTHESIA WITH XYLAZINE PREMEDICATION AND REVERSAL WITH AMINOPHYLLINE IN DOGS** is a bonafide record of research work done by me during the course of research and that the thesis has not previously formed the basis for the award to me of any degree, diploma, associateship or other similar title, of any other university or society.

Mannuthy,
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CERTIFICATE

I hereby declare that this thesis entitled **TILETAMINE-ZOLAZEPAM ANAESTHESIA WITH XYLAZINE PREMEDICATION AND REVERSAL WITH AMINOPHYLLINE IN DOGS** is a record of research work done independently by Mrs. MINI BHARATHAN under my guidance and supervision and that it has not previously formed the basis for the award of any degree, fellowship, or associateship to her.

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Dedicated

to the memory of my father

and

to my mother

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Introduction

INTRODUCTION

Anaesthetics include a field of pharmacology which has undergone considerable development during the past two decades. The state of general anaesthesia is a drug induced absence of perception of all sensations. Anaesthesia necessitates the administration of doses of drugs in such a manner as to produce the desired effects and avoid undesirable side-effects or toxicity.

Considerable emphasis has been given in the recent past to intravenous anaesthesia in routine surgical practice, especially in the Veterinary field. The ease of administration of drugs, rapid induction, smooth recovery, and high efficacy and safety provided by combinations of drugs have been the main reasons for this. Among the intravenous general anaesthetics, the dissociative anaesthetics have attracted very good attention. The important members of this group - phencyclidine, ketamine and tiletamine having 'aryl cyclohexylamine' structure, produce the characteristic 'dissociative anaesthesia' (Short, 1989).

Tiletamine (CI-634), one member of the group of dissociative anaesthetics, was synthesised in 1968. Tiletamine HCl is chemically 2-(ethyl-amino)-2-(2-thienyl) cyclohexanone HCl.

Tiletamine, when used alone, does not provide adequate relaxation of abdominal muscles and the cataleploid anaesthesia is accompanied by convulsive seizures and clonic muscular reactions. In order to eliminate the bad effects, combination of tiletamine with non phenothiazine pyrazolo-diazepinone tranquilizer zolazepam (CI-716) or flupyrazapon was developed. Chemically, zolazepam HCl is 4(-0-fluorophenyl) 6,8-dihydro- 1,3,8, trimethyl pyrazolo-3, $3e_1$, 4 diazepam-7(14)-One HCl.

The combination was found to be useful for the induction of anaesthesia prior to inhalant anaesthetics or as a sole anaesthetic agent for a wide variety of diagnostic and surgical procedures. But at low dose levels (less than 5 mg/kg body weight), the combination did not induce muscle-relaxation and analgesia sufficient for surgery, in dogs.

Xylazine, an alpha-2 agonist and a non-narcotic sedative analgesic is compatible with most drugs and strongly potentiates the effects of sedatives, tranquilizers, and dissociative anaesthetics. Studies in swine (Thurmon et al., 1988), calves (Thurmon et al., 1989) and horses (Hubbel et al., 1989) show that when xylazine is combined with tiletamine-zolazepam combination, it enhances the anaesthetic and analgesic effects of the latter.

Respiratory depression and prolonged anaesthesia are two hazards commonly associated with the use of injectable anaesthetics. It is often desirable to have a drug that can be used to antagonize the anaesthetic agent when necessary to alleviate the respiratory depression and to hasten recovery.

Aminophylline (theophylline ethylene diamine) is a methylxanthine derivative that acts as a potent CNS and respiratory stimulant. Aminophylline has been found to reverse the narcosis induced by morphine (Gilman et al., 1991) and anaesthesia produced by the tiletamine-zolazepam combination in dogs (Hatch et al., 1988).

The present study was therefore undertaken with the following objectives

(1) to study the synergistic effect of xylazine with tiletamine-zolazepam anaesthesia

(2) to study the reversing effect of aminophylline in tiletamine-zolazepam-xylazine anaesthesia in dogs.

The result of this study will help the practicing veterinarians to formulate a new and effective anaesthetic combination for their surgical practice, and they will find the combination to be a significant addition to their anaesthetic options.

Review of Literature

REVIEW OF LITERATURE

Initially the dissociative anaesthetics were introduced in Veterinary Medicine solely as induction or immobilizing agents. But now they are often used in combination with muscle-relaxants, sedatives, tranquilizers and analgesics to produce CNS depression sufficient to perform surgical procedures. Tiletamine, one of the members of this group of dissociative anaesthetics, was discovered by the Experimental Therapeutics Division of Parke-Davis and Company in 1968 in an effort to identify a neuropharmacological agent with potency and duration of effect intermediate to those of phencyclidine and ketamine.

2.1. Tiletamine

Chen and Bohner (1968) have reported that satisfactory surgical anaesthesia can be achieved in rabbits with a cataleptic dose of tiletamine (CI-634) given intramuscularly (20 mg/kg) followed by intra venous chloral hydrate after two or three minutes at a dose rate of 250 mg/kg. CI-634 not only produced immobilization that made intravenous injection of a large volume of solution an easy manoeuvre, but also enhanced the depth and duration of chloral hydrate anaesthesia.

Chen and Ensor (1968) investigated the pharmacological properties of the drug (CI-634). They could produce a calming (taming) to cataleptic (incapacitating) effect in cats at small dose levels and general anaesthesia at large dose levels. Both oral and intramuscular routes of administration were used to produce calmness and catalepsy. Intramuscular route of administration was used to produce general anaesthesia. Decreased motor activity, lack of resistance to jaw opening and loss of biting reflex were the signs of the calming effect. Loss of body righting reflex without head-drop was the sign of catalepsy. Analgesia to pinpricking and to foot-pad pinching and unconsciousness were the signs of surgical anaesthesia which lasted for one to two hours. They found that the safe anaesthetic dose range of Tiletamine in cats was 15 to 100 mg/kg intramuscularly.

Bennett (1969) observed that CI-634 intramuscularly in cats produced satisfactory anaesthesia with a rapid onset of action and wide safety margin. However, he reported that muscle relaxation was not adequate for routine surgical procedures and that inhalation of methoxyflurane could be used to produce good muscle relaxation.

Chen et al. (1969) stated that CI-634 at doses of 20-100 mg/kg body weight produced surgical anaesthesia in monkeys and cats, while in dogs, it produced either light anaesthesia or transitory clonic seizures. They found that catalepsy was the characteristic effect of CI-634 in all animal species. They concluded that the drug due to its rapid onset of action, high cataleptic potency, and wide safety margin was useful for immobilization of wild animals and as a preanaesthetic agent.

Garmer (1969) found that, when CI-634 was injected intra-muscularly in doses of 0.5 to 30 mg/kg body weight, individual cats varied greatly in their response, making it difficult to predict the depth and duration of narcosis. In small doses, however, the drug was found to be useful as a sedative.

Calderwood et al. (1971) investigated the cardio-respiratory effects of tiletamine in cats when given intra muscularly at a dose rate of 11 mg/kg. Blood pressure, heart rate, acid base status and oxygen tension were determined for six hours. They observed that the drug produced the typical clinical manifestations of a 'dissociative anaesthetic state'. They concluded that the drug caused significant respiratory depression without any cardiovascular change.

Bree (1972) studied the use of tiletamine as an anaesthetic in six non human primate species. After an intramuscular injection of tiletamine (3 to 4 or 5 to 6 mg/kg) induction of anaesthesia was smooth and occurred in one to three minutes. Though the mean 'sleeping time' varied greatly among the different species, recovery from anaesthesia was smooth and uncomplicated in all the cases.

2.2. Tiletamine-Zolazepam Combination

The inadequate muscle relaxation produced by tiletamine led to the development of a more effective combination of tiletamine with a non-phenothiazine diazepinone tranquilizer 'zolazepam' which has excellent anticonvulsant and muscle-relaxant effects.

Bree et al. (1972) reported the results of clinical evaluation of CI-744 (combination of tiletamine HCl and flupyrazapon or zolazepam HCl) in dogs and primates. The drug combination was administered at a dose rate of 6-12 mg/kg body weight and 2-6 mg/kg body weight respectively. They found that the drug combination was useful as a general anaesthetic in these species with a rapid and smooth induction, dose related duration of anaesthesia and smooth and uneventful recovery.

Connel et al. (1974) found CI-744 suitable as a general anaesthetic for sheep at a dose range of 9-14 mg/kg when given intravenously. Induction was very smooth and rapid (15-30 seconds) and the mean duration of anaesthesia was three to four hours

Gray et al. (1974) did experiments with various species of zoo animals and revealed that CI-744 produced a tranquil state in small doses and anaesthesia with large doses. The drug was administered by means of a "Capchur gun". The dosage and uses of CI-744 in various species of zoo animals were tabulated by them.

Schulz and Fowler (1974) found that CI-744 was effective as a safe anaesthetic in chinchilla rabbits (Chinchilla villidera). The drug was injected intramuscularly at dose rate of 3.3 to 110 mg/kg body weight. Induction was rapid and smooth and ranged from 1-5 minutes and duration of recumbency ranged from 53 to 833 minutes depending on the dose of drug administered.

Ward et al. (1974) tested the drug combination in sheep, dogs, cats, rats, guinea pigs, pigeons and rabbits. Except for pigeons, the drug was found to have a wide safety margin. It induced satisfactory anaesthesia for surgical procedures lasting 30-60 minutes at a dose rate of 13 mg/kg

in sheep, 6-13 mg/kg in cats and dogs and 20-30 mg/kg in rats Although useful for restraint of guinea pigs and rabbits, lack of muscle relaxation and response to external stimuli in these species, made CI-744 unsatisfactory for anaesthesia.

Smith and Pettway (1975) demonstrated that CI-744 did not sensitize the hearts of dog or cats to epinephrine-induced ectopic ventricular fibrillation. They anesthetized dogs and cats with CI-744 at intramuscular doses of 20 mg/kg and then treated them with increasing doses of epinephrine intramuscularly to find out the arrhythmogenic dose of epinephrine. The results proved that animals anaesthetized with CI-744 did not exhibit increased sensitivity of myocardium to epinephrine.

Boever et al. (1977) used CI-744 for chemical restraint and anaesthesia in wild and exotic carnivores. They observed that the anaesthesia produced by CI-744 was characterised by a rapid induction, excellent analgesia and good muscle relaxation at high doses and was followed by smooth and safe recovery.

King et al. (1977) reported that the tiletamine-zolazepam combination was useful for the immobilization of

wild lions and leopards with an anaesthetic pattern similar to that associated with the use of other irreversible intramuscular anaesthetics like ketamine. Lions were found to be more susceptible than leopards and males more so than females. The doses of the drug were based on body weight. There was a significant positive linear relationship between the duration of anaesthesia and dosage for all animals.

Booker et al. (1982) studied the cardiodynamics in the rhesus macaque during dissociative anaesthesia produced by tiletamine-zolazepam at an intramuscular dose rate of 1.5 to 3 mg/kg body weight. They noted that the drug combination did not have pronounced or prolonged cardiovascular effects and so can be used for minor surgery and restraint during physiological studies.

Silverman et al. (1983) evaluated the drug combination in laboratory rodents. They found that the drug produced satisfactory anaesthesia and analgesia in rats when given intraperitoneally and intramuscularly at dose rates of 20 mg/kg and 40 mg/kg body weight respectively. It produced anaesthesia, but not analgesia at dose rates of 100-160 mg/kg body weight and 50-80 mg/kg body weight respectively in mice and hamsters. Thus it was found that CI-744 was an effective anaesthetic for rats, but not for mice or hamsters.

Haigh et al. (1985) tried to immobilize polar bears (Ursus maritimus phipps) with the tiletamine-zolazepam combination. The mean dose for satisfactory immobilization with a single injection was found to be 5.1 mg/kg with a mean induction time of 5.1 minutes and a duration of anaesthesia of 2 hours. Preliminary results indicated that the bears did not have respiratory depression and were able to thermoregulate while immobilized but analgesia was not satisfactory.

Schobert (1987) summarized the dose ranges of Telazol (Tiletamine-zolazepam combination) used clinically for restraint or anaesthesia of 75 wild and exotic species of animals. He also revealed certain advantages of using Telazol over other immobilizing or anaesthetic regimen in exotic species which included the small volume dose requirements due to high solubility, ease of preparation of solution, rapid induction, dose-related restraint ranging from chemical immobilization to cataleptiform anaesthesia, good to excellent muscle relaxation, an apparently wide safety margin and a generally unremarkable recovery.

Genevois et al. (1988) made a comparative study of the effects of xylazine-ketamine and tiletamine-zolazepam combinations on certain physiological functions in dogs. During the anaesthesia period of 45 minutes, variations in

rectal temperature, respiratory and cardiac rates, blood pressures partial pressure of O_2 (pO_2), partial pressure of CO_2 (PCO_2), bicarbonate, pH and arterial O_2 saturation were recorded. They found that both anaesthetics produced hypothermia, reduction of blood pressure and respiratory depression. Changes in blood gases and acid-base equilibrium were found to be similar in both the anaesthesias.

Tracy et al. (1988) conducted trials to compare the effects of intravenous and intramuscular administration of Telazol in dogs and cats. With a single dose rate of 9.9 mg/kg and 12.8 mg/kg body weight in dogs and cats respectively, it was found that the intravenous route gave a faster induction to recumbency and anaesthesia and a greater certainty of anaesthesia to nociceptive stimuli, than the intramuscular route. The only difference in the quality of anaesthetic induction was that the intravenous route did not produce any degree of ataxia because dogs and cats became recumbent in a few seconds.

Donaldson et al. (1989) described the effect of testing low doses of intravenous Telazol in canine practice. They gave Telazol at doses of 2 and 1 mg/kg body weight and studied the physiological changes and anaesthetic characteristics produced by the drug. Physiological changes

included increased heart rates and altered ventilatory patterns, including a brief period of apnoea. All the dogs became recumbent within one minute, retained active palpebral reflexes and had a mean anaesthesia time of 22.7±7.3 and 11.9±6.6 minutes after single doses of 4 mg/kg or 2 mg/kg of Telazol, respectively. It was inferred that low doses of Telazol were safe and effective as induction agents prior to inhalant anaesthesia or as a chemical restraint agent for relatively painless procedures in dogs.

Fieni et al. (1989) administered Telazol intravenously with atropine premedication (0.05 mg/kg subcutaneous) to two batches of young healthy dogs and one batch of dogs in poor general condition. All the three batches received intravenous Telazol at a dose rate of 10 mg, 5 mg and 5 mg/kg body weight respectively for induction and 10, 5 and 2.5 mg/kg body weight respectively for the maintenance of anaesthesia. In all the cases, satisfactory anaesthesia could be produced with an average duration of 31-47 minutes. Thus tiletamine-zolazepam combination was found to be well adapted to canine anaesthesia through the intravenous route particularly in the high risk patients, where it could be an alternative to gaseous anaesthesia.

Hellyer et al. (1989) evaluated the anaesthetic, hemodynamic and respiratory effects of Telazol in dogs. They reported that the drug at dose rate of 6.6, 13.2 and 19.8 mg/kg produced satisfactory anaesthesia with rapid induction and a dose dependent duration. The combination also produced significant increases in cardiac output, arterial blood pressure and left ventricular pressure. Peripheral vascular resistance and minute ventilation were decreased significantly only after the 19.8 mg/kg dose.

Lin et al. (1989) studied the hemodynamic response of calves to tiletamine-zolazepam anaesthesia. The drug combination was given at a dose rate of 4 mg/kg following isoflurane anaesthesia. The values for cardiac output, cardiac index, stroke index and central venous pressure did not change significantly. The systolic, mean and diastolic arterial blood pressure and systemic vascular resistance were significantly decreased below baseline at 5 minutes, but increased above the baseline at 20 minutes and remained so throughout the experiment. They concluded that the hemodynamic changes induced by tiletamine-zolazepam were minimum and were compatible with safe anaesthesia in calves.

Loughlin and Spraker (1989) immobilized 29 female northern sea lions (Eumetopias jubatus) using Telazol in

dosages ranging from 1.8 to 8.1 mg/kg. Best results were achieved with dosages ranging between 1.8 and 2.5 mg/kg which resulted in smooth induction and recovery. It was concluded that the combination was highly useful as immobilization agents for the female northern sea lions.

Stirling et al. (1989) demonstrated that polar bears (Ursus maritimus) could also be immobilized with tiletamine-zolazepam at a dose rate of 8-9 mg/kg body weight. The drug was found to produce rapid immobilization with satisfactory analgesia and faster recovery. There was a wide safety margin and bears appeared to be able to thermoregulate while immobilized.

Taylor et al. (1989) determined the effective dose of tiletamine-zolazepam combination needed to immobilize free ranging grizzly bears (Ursus arctos horribilis) by darting from a 'capchur gun'. Use of the recommended dose for immobilizing grizzly bears (7-9 mg/kg) resulted in a mean induction time of 4.0±2.8 minutes and a safe handling period of 45-79 minutes. The side effects included excessive salivation and brief tremors. They concluded that the drug combination was excellent for immobilization of grizzly bears because of rapid induction, timely and predictable recovery, wide safety margin and few adverse side-effects.

Baker et al. (1990) stated that the tiletamine-zolazepam combination, at a dose rate of 1 mg/kg was safe and reliable for immobilizing wild gray seals (Halichoerus grypus) and southern elephant seals (Mirouga leonina) and that the drug had a number of advantages over all the other agents used previously.

Bednarski and Muir (1990) determined the ventricular arrhythmogenic dose of epinephrine (ADE) in dogs with halothane alone and with halothane after injection of tiletamine-zolazepam. The ADE was the same during anaesthesia with halothane alone and when injection of tiletamine-zolazepam preceded administration of halothane. Thus they confirmed that the administration of tiletamine zolazepam did not alter the ADE in dogs anaesthetized with halothane, and hence the drug may be a useful adjuvant in dogs or cats susceptible to the development of catecholamine induced ventricular arrhythmias.

Bocard (1990) made a comparative study of three anaesthetic protocols in cats: Ketamine + acepromazine, Ketamine + diazepam and tiletamine + zolazepam (Zoletil). He found that the quality and duration of anaesthesia and muscle relaxation were best with Zoletil, though respiratory depression was more pronounced and longer with this

combination. He also reported that zolazepam was superior to diazepam and acepromazine in preventing the myotonia induced by aryl-cyclohexylamines.

Bush et al. (1990) tried the drug combination for anaesthetizing free-ranging male koalas and some selected marsupials in captivity. The drug combination given at a dose range of 5 to 7.7 mg/kg body weight, produced a surgical plane of anaesthesia, lasting 30 to 45 minutes. There was no depression of heart-rate or respiration.

Brammer et al. (1991) made studies on the anaesthetic effect of the drug combination in New Zealand White rabbits. Telazol was injected intra muscularly at the rate of 32 or 64 mg/kg body weight and the depth and duration of anaesthesia were monitored. At both the doses, righting reflex was lost within 2 minutes post-injection, but the animals responded to noxious stimuli for the entire duration of anaesthesia. BUN and serum creatinine levels were found to increase one day post-injection and continued steady throughout the week with a correlated elevation in urine protein. It was concluded that the drug combination did not produce analgesia in rabbits and was nephrotoxic at both 32 and 64 mg/kg dose levels and therefore, could not be used in rabbits.

Codner and McGrath (1991) proved that tiletamine-zolazepam anaesthesia had no effect on the response to intradermally administered histamine in dogs. They injected various concentrations of histamine intradermally in clinically normal dogs before and after the administration of the drug combination (4 mg/kg, intra venous). They found that Telazol had no effect on the size of wheals produced and that the short acting chemical restraint produced by the drug combination facilitated the intradermal testing procedure.

Hess (1991) tested the drug combination for its effect at a dose rate of 10 mg/kg intramuscularly on hemodynamics, respiration and the antagonistic effect of flumazenil. The drug was found to cause a highly significant increase in heart rate and slight decrease in both the mean arterial blood pressure and arterial PO_2. The drug also showed electro-stabilizing and antifibrillatory properties even in the presence of severe arrhythmias. The benzodiazepine compound of the drug combination could be antagonized by flumazenil.

Lagutchik et al. (1991) assessed the effect of the drug combination in ewes at doses of 12 and 24 mg/kg intra-venously. The hemodynamic, pulmonary and ventilatory variables were neasured at 15 minute intervals upto 120

minutes. Immediate drug effects included apnoea, decreased mean arterial blood pressure and arterial hypoxemia. Cardiac output decreased and systemic vascular resistance increased significantly. Both drug dosages induced apneustic breathing patterns and caused significant changes in arterial and venous blood Hb concentrations and PCV. Because of the alternations in cardiopulmonary functions, they cited that the drug combination could not be used in studies requiring minimal effects on heart and lung function.

2.3. Tiletamine-Zolazepam-Xylazine

Thurmon et al. (1988) studied the effect of Telazol alone and Telazol-xylazine combination in pigs. They found that Telazol alone induced immobilization, but did not induce muscle relaxation and analgesia sufficient for surgery. So they tried a combination of xylazine (1.1 to 2.2 mg/kg) and Telazol (6 mg/kg) in order to produce satisfactory surgical anaesthesia. They observed that adding xylazine to this combination not only yielded a measurable sedative, analgesic effect, but also simplified administration and maintenance of anaesthesia by allowing rapid intubation.

Hubbell et al. (1989) tried the combination of tiletamine-zolazepam and xylazine in horses. They gave the combination at dose rates of 1.1 mg/kg and 2.2 mg/kg intravenously, 10 minutes after the intramuscular administration of xylazine at the same dose rate to horses. Xylazine was found to decrease the heart-rate, respiratory rate and cardiac output and increase central venous pressure and mean pulmonary arterial pressure 5 minutes after administration. Telazol administration caused decrease in arterial pO_2, arterial pH and increase in arterial pCO_2 and these changes persisted for the entire duration of recumbency. Induction was rapid and smooth and the recovery was smooth and uneventful. Thus they found that xylazine was effective as a complementary drug to induce reasonably safe, short-term anaesthesia in horses.

Ruppert (1989) stated that tiletamine-zolazepam was a suitable anaesthetic for intra muscular administration for adult pigs, but inadequate for piglets due to insufficient analgesia and violent recovery. He also reported that adequate analgesia and smoother recovery could be provided by combining the combination with meditomidine (an alpha-2 agonist) at a dose rate of 0.1 mg/kg body weight.

Thurmon et al. (1989) used combination of xylazine and tiletamine-zolazepam in calves and found to produce excellent anaesthesia at doses of 0.1 to 0.2 mg/kg xylazine and 4 mg/kg Telazol. There was rapid induction (60-120 seconds), satisfactory duration of anaesthesia, good analgesia and safe and smooth recovery. Heart-rate and respiratory rates remained within clinically acceptable limits.

Abrahamsen et al. (1991) found that in horses, tiletamine-zolazepam anaesthesia with xylazine premedication gave a rapid and smooth induction with sufficient muscle relaxation.

Lin et al. (1991) studied the hemodynamic response of calves to tiletamine-zolazepam-xylazine anaesthesia. The calves were anaesthetized with isoflurane and instrumented for hemodynamic studies. Baseline values were recorded following recovery from isoflurane. Immediately after that, tiletamine-zolazepam (4 mg/kg) and xylazine (0.1 mg/kg) were administered intravenously. Values were again recorded at 5, 10, 20, 30, 40, 50 and 60 minutes after injection. Changes in the left ventricular stroke work index, PO_2 and arterial pH were insignificant. Arterial and systemic vascular resistance increased above baseline at 5 minutes

and then gradually decreased below baseline at 40 minutes. Heart rate, cardiac output and cardiac index were decreased at 5 minutes and with the exception of cardiac output, remained so for 60 minutes. Cardiac output turned to baseline value at 30 minutes. All calves recovered without complications. It was concluded that tiletamine-zolazepam-xylazine was a safe and useful anaesthetic regimen in calves.

Wan et al. (1992) compared the responses to the drug combinations-xylazine-ketamine (1.1 and 2.2 mg/kg respectively) and detomidine-tiletamine-zolazepam (0.04 and 1.1 or 1.4 mg/kg respectively) in horses. The duration of analgesia and the times to sternal recumbency and standing positions were recorded. The duration of analgesia was found to be significantly greater with detomidine-tiletamine-zolazepam than with xylazine-ketamine. Arterial pressure was significantly higher and PO_2 lower during anaesthesia with detomidine-tiletamine-zolazepam. Thus detomidine-tiletamine-zolazepam was proved to provide comparable anaesthesia of a longer duration than ketamine-xylazine.

2.4. Reversal of Tiletamine-zolazepam anaesthesia

Respiratory depression and prolonged anaesthesia are associated with the use of injectable anaesthetics.

Therefore, agents that would antagonize anaesthesia without ill-effects on heart rate, body temperature or behaviour have to be available for prompt reversal of anaesthesia. Hatch et al. (1988) tried 12 drugs as antagonists which included 4-aminopyridine (4-AP), yohimbine, doxapram, naloxone, Ro 15-1788, aminophylline, physostigmine, neostigmine, dexamethasone, tolazoline, choline and metoclopramide. Telazol at a dose rate of 30 mg/kg was administered intramuscularly after 30 minutes following intramuscular glycopyrrolate injection (0,011 mg/kg). After one hour, single dose of the various antagonist drugs were given intravenously. Time of onset of anaesthesia, arousal time, walk time, temperature, heart rate and respiratory rate were recorded. Of the 12 drugs tested, 4-AP, Yohimbine, doxapram, naloxone, Ro 15-1788, aminophylline and neostigmine increased respiratory rates and out of these, only doxapram and Ro 15-1788 caused rapid arousal. Generalized muscle rigidity occurred in the dogs given Ro 15-1788. It was concluded that doxapram at a dose of 5.5 mg/kg produced prompt arousal without relapse or any undesirable side effects.

Bednarski et al. (1989) investigated the effects of tolazoline, doxapram and Ro 15-1788 on the depressant action of Telazol in dogs and cats. Telazol was administered

intravenously at the rate of 10 mg/kg for dogs and 5 mg/kg for cats. After 30 minutes, one of the three antagonists was injected intravenously. The arousal time, time to sternal recumbency, time to walking, heart rate, respiratory rates, body temperature and behavioural characteristics were recorded. The results indicated that only Ro 15-1788 significantly shortened the recovery time in dogs, while arousal time in cats was shortened following Ro 15-1788 and doxapram.

Materials and Methods

MATERIALS AND METHODS

3.1. Experimental Animals

Thirty adult apparently healthy mongrel dogs of either sex weighing between nine and nineteen kilograms were used for the study. They were observed for their general health for 10 days before experimentation and maintained on an identical diet. Food was withheld for 12 hours before experimentation, to minimise emesis, regurgitation and aspiration of stomach contents during anaesthesia. Water was given ad libitum. Dogs were randomly assigned to five treatment groups, each group containing both male and female dogs.

3.2. Drugs

1. Tiletamine-zolazepam* - 500 mg vial containing 250 mg tiletamine HCl + 250 mg zolazepam HCl was reconstituted with 5 ml of the solvent so that the final solution contained 100 mg/ml of the active drug.

   Another product available for use is TELAZOL**

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* Zoletil - Virbac Pharmaceuticals, France.

** Telazol - A.H. Robins Company - containing 250 mg tiletamine HCl + 250 mg Zolazepam HCl.

2. Xylazine[1] solution - Each ml containing 20 mg xylazine base.

3. Atropine[2] sulphate solution 1 ml ampoule containing 0.6 mg atropine sulphate.

4. Aminophylline[3] injection - 10 ml ampoule containing 25 mg Aminophylline/ml.

3.3. Treatment

Drugs were given at the same time each morning. All the dogs were given subcutaneous injections of atropine sulphate at a dose of 0.05 mg/kg body weight, to prevent excessive peripheral cholinergic effects of drugs without interfering with CNS mechanisms. The treatment schedule undertaken was as given below.

First group of six animals (C) received atropine sulphate premedication and after fifteen minutes, tiletamine-zolazepam was administered intravenously at a dose rate of 5 mg/kg body weight.

Second group (T_1) of six animals received xylazine at a dose rate of 0.5 mg/kg body weight intramuscularly along with atropine. Fifteen minutes later, Zoletil was given intravenously at a dose rate of 2.5 mg/kg body weight.

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1. XYLAZINE - Farvet Laboratories, Holland.

2. ATROPINE SULPHATE INJECTION - The Moriengers Chemical Laboratories, Calcutta

3. AMINOPHYLLINE INJECTION - Remedy Pharmaceuticals, Calcutta.

Third group (T_2) of six animals received xylazine at a dose of 1 mg/kg body weight intramuscularly along with atropine. Fifteen minutes later, Zoletil was given intravenously at a dose rate of 1.25 mg/kg body weight.

Table 1. The treatment schedule for each group of animals:

Group	Zoletil dosage mg/kg	Xylazine dosage mg/kg	Aminophylline dosage (mg/kg)
C (Control)	5	-	-
T_1	2.5	0.5	-
T_2	1.25	1	-
T_3	1.25	1	20
T_4	1.25	1	40

The studies in groups T_1 and T_2 indicated that the group T_2 resulted in a longer duration of anaesthesia. Hence this dose schedule was chosen for the study in the subsequent groups(ie. T_3 and T_4).

Fourth group (T_3) of animals received the same treatment as in T_2. Time of appearance of skin clamp anaesthesia was noted. After 8 minutes (ie. at the middle of anaesthesia) aminophylline was administered at a dose rate of 20 mg/kg intravenously.

Fifth group (T_4) of animals received the same treatment as in T_2. Time of appearance of skin clamp anaesthesia was noted and after eight minutes, aminophylline was administered at a dose rate of 40 mg/kg body weight intravenously.

To evaluate surgical anaesthesia, 2 methods of nociceptive stumuli were used after the animals became recumbent. A skin clamp was used to simulate sensation produced by soft tissue surgery of the skin and sub cutaneous tissues. To accomplish this, an Allis tissue forceps was clamped as tightly as possible to a fold of skin (incorporating the sub cutis) at a site immediately posterior to the mid-point of the last rib.

The other stimulus, a tail clamp was used to produce a higher degree of nociception. For this, another Allis forceps was clamped firmly but carefully over a tail segment incorporating a coccygeal vertebra. These stimuli were applied when the animal reached recumbency and continued at three minute intervals until any response to the stimuli were observed.

The ear twitch reflex (evinced by a twitch of the ear when an Allis forceps is clamped to the ear tip) and the pedal reflex (shown by a sudden withdrawal of the leg when

the interdigital web is pinched) were also tested at two or three minute intervals.

Actual times of injection of tiletamine-zolazepam recumbency, beginning and end of skin clamp anaesthesia beginning and end of tail clamp anaesthesia, disappearanc and reappearance of pedal reflex and ear twitch reflex, holding head high, sternal recumbency, standing and walking were recorded. The following times were computed in all treatments.

1. Time from injection of tiletamine-zolazepam to the appearance of skin clamp anaesthesia ie. the induction time.

2. Time from injection to the beginning of tail clamp anaesthesia.

3. Duration of skin clamp anaesthesia ie. time from the beginning of skin clamp anaesthesia to the end of skin clamp anaesthesia.

4. Duration of tail clamp anaesthesia ie. time from the beginning of tail clamp anaesthesia to the end of tail clamp anaesthesia.

5. Time from recumbency to the beginning of righting (head initially raised from the floor).

6. Time from recumbency to standing

7. Time from recumbency to walking or the duration of Zoletil effect.

8. Time from the end of skin clamp anaesthesia to walking or the recovery time.

Behavioural characteristics that were remarkable and repetitive were noted before and following Zoletil administration and subsequent to the administration of antagonist.

Before drug injection, baseline values (time=0) were recorded for heart rate respiration rate and rectal temperature. At 5, 10, 20, 30, 45, 60, 90 and 120 minutes after drug injection, values for these variables were again recorded.

Haematological parameters like total RBC count, total and differential WBC count, haemoglobin concentration, erythrocyte sedimentation rate (ESR) and packed cell volume (PCV) were assessed for blood samples taken before anaesthesia, at the middle of anaesthesia (about 8 minutes after the beginning of skin clamp anaesthesia) and after anaesthesia (about 10 minutes after sternal recumbency).

Total erythrocyte count, total and differential leukocyte counts, the haemoglobin concentrations, the PCV and the ESR were estimated according to the techniques described by Wintrobe et al. (1981).

The data were analysed statistically using a one-way analysis of variance for assessing the differences within the groups and between the groups.

RESULTS

The results of the experiments are presented in tables 2-7 and figures 1-5.

4.1.Anaesthesia

The animals became recumbent within a mean time of 13.3 seconds for the control group and 15.8 seconds for group T_1 after the administration of Zoletil. All the animals in group T_2, four of the animals in group T_3 and three of the animals in group T_4 became recumbent 8-10 minutes after the administration of xylazine and before the administration of Zoletil. The average time of recumbency of the remaining animals in groups T_3 and T_4 were 6.7 and 9.2 seconds respectively. Statistical analysis revealed no significant difference in the time of recumbency between the different groups.

The time of appearance of tail clamp anaesthesia for the groups C, T_1, T_2, T_3 and T_4 are 4.5, 5.2, 4.0, 2.7 and 2.8 minutes respectively. There is no significant difference in the values between the groups, on statistical analysis.

The mean time of appearance of skin clamp anaesthesia for the five groups were 8.8, 8.7, 7.5, 4.7 and 4.8 minutes respectively. These values also showed no significant difference between the groups.

The time of abolition or disappearance of tail clamp anaesthesia (reappearance of tail clamp reflex) for the different groups C, T_1 and T_2 were 23.5, 20.2 and 18.6 minutes respectively and for the groups T_3 and T_4 were 14.2 and 15.7 minutes respectively. On statistical analysis significant difference could be seen to exist between the groups C and T_2. There was significant difference between T_2 and T_3 also in the time of reappearance of the tail clamp reflex.

The end of skin clamp anaesthesia (reappearance of skin clamp reflex) was noticed at 29.5, 23.3 and 22.7 minutes for the groups C, T_1 and T_2 respectively and at 14.8 and 16.7 minutes for the groups T_3 and T_4 respectively. These values were found to be significantly different between the groups C and T_2. There was significant difference between T_2 and T_4 also in the time of abolition of skin clamp anaesthesia.

The mean time of regain of righting reflex for the groups C, T_1 and T_2 were 23.8, 28.8 and 35.3 minutes respectively and for the groups T_3 and T_4 were 24.0 and 24.8 minutes respectively. These values also showed significant difference between the groups C and T_2. The time of regain of righting reflex was also significantly different between T_2 and T_3 and T_4.

The mean time for sternal recumbency for the groups C, T_1 and T_2 were 42.8, 33.2, 43.3 minutes respectively and for the groups T_3 and T_4 were 28.5 and 29.8 minutes respectively. Highly significant difference was found to exist between the groups T_2 and T_3 and T_4 and significant difference could be seen between the groups C and T_2 also.

The mean time for standing were 73.3, 48.0, 47.5, 41.3 and 39.5 minutes respectively for the groups C, T_1, T_2, T_3 and T_4. The corresponding values for the time for walking were 78.2, 50.8, 48.3, 42.2 and 40.8 minutes respectively. There was no significant difference between the groups T_2, T_3 and T_4, but there was significant difference between the groups C and T_2.

The induction time (time from injection of tiletamine zolazepam to the appearance of skin clamp anaesthesia), duration of skin clamp anaesthesia and the recovery time (time from the end of skin clamp anaesthesia to sternal recumbency) for the group C were 8.8, 20.5 and 13.5 minutes respectively. The corresponding values for the group T_1 were 8.7, 14.0 and 10.0 minutes, for the group T_2 were 9.2, 15.2 and 20.7 minutes, for the group T_3 were 2.8, 10.1 and 13.7 minutes and for the group T_4 were 4.8, 11.9 and 13.1 minutes respectively. These values were found to be significantly shorter for the groups T_3 and T_4 when compared

to T_2. The total duration of Zoletil effect (ie. the time from the beginning of sternal recumbency to walking after anaesthesia) for the five groups were 78.2, 50.8, 48.3, 42.2 and 40.8 minutes respectively.

The ear twitch reflex disappeared almost immediately after the administration of Zoletil. Though 2 of the dogs in the control group and one each in the groups T_1 and T_3 did not show active ear twitch reflex even after recovery, the ear twitch reflex of the remaining animals reappeared after mean time of 30.8, 23.4, 29.8, 21.6 and 22.7 minutes for the groups C, T_1, T_2, T_3 and T_4 respectively. All the animals in group C and 4 animals in group T_1 showed active pedal reflexes throughout the period of anaesthesia. The mean time of reappearance of pedal reflex (lost immediately after the administration of Zoletil) for the groups T_1, T_2, T_3 and T_4 were 21.5, 28.5, 20.5 and 19.0 minutes respectively.

Recovery in the first group was characterised by progressively increasing motor activity, which was especially evident in the cervical muscle as rhythmic head and neck rocking. This activity continued until the dogs attained sternal recumbency and was absent in groups T_1, T_2, T_3 and T_4. Paddling and whining were also seen in the control group.

4.2. Rectal Temperature

The rectal temperature showed a gradual increase from an initial value of 101.1°F before anaesthesia to 102.5°F in 10 minutes time in group C. After that the temperature showed a steady decrease to 100.9°F in 30 minutes. From 45 minutes onwards, the temperature again increased to 102°F in 90 minutes time. For the groups T_1, T_2, T_3 and T_4 the baseline (time-0) temperatures which where 102.2, 101.9, 101.4 and 101.3°F respectively showed a gradual decrease to 101.2, 101.2, 100.6 and 100.9°F respectively in 30 minutes time and then increased gradually to 101.4, 101.5, 101.6 and 101.2°F respectively in 90 minutes time. Statistical analysis revealed no significant difference in the rectal temperatures between the different groups throughout the experiment, except at 10 minutes time. At 10 minutes, the decrease in body temperature was significantly greater for T_3 and T_4, when compared to T_2.

4.3. Pulse Rate

The pulse rate which was 21, 18, 19, 20 and 19/15 seconds respectively for the groups C, T_1, T_2, T_3 and T_4 before anaesthesia showed a steady increase to 43, 32, 36, 32 and 34/15 seconds respectively, 15 minutes after anaesthesia. Later these values decreased gradually to near pre-injection values of 24, 20, 21, 20 and 24/15 seconds

respectively in 120 minutes time. Statistical analysis revealed no significant difference between the groups in the pulse rate at 0, 5, 10, 20, 30, 45, 60, 90 and 120 minutes during anaesthesia. But the increase in pulse rate at 15 minutes was found to be significantly greater with the group C when compared to T_2.

4.4. Respiration Rate

The respiration rate decreased progressively from mean base line values of 11, 13, 8 and 8/15 seconds respectively for the groups T_1, T_2, T_3 and T_4 to mean values of 3, 3, 4 and 3/15 seconds respectively in 10 minutes time. Thereafter, these values increased gradually to mean values of 15, 18, 9 and 9/15 seconds respectively in 120 minutes time. In the control group, the pre-injection value of 12/15 seconds decreased to 8/15 seconds after 5 minutes and this remained almost steady for the next 40 minutes and then progressively increased to 33/15 seconds in 120 minutes. The trend in the respiratory rate showed no significant difference before anaesthesia and after 30 minutes following induction of anaesthesia. But from 5 to 30 minutes during anaesthesia, the decrease in respiration was found to be significantly greater for the group T_2 when compared to group C ie. T_2 produced a more profound decrease in respiration rate when compared to C.

4.5. Haematology

The RBC count before, during and after anaesthesia for the group C were 5.9, 4.4 and 6.9 millions/cu.mm respectively, for the group T_1 were 5.6, 5 and 5.5 millions/cu.mm respectively, for the group T_2 were 5.5, 4.3 and 5 millions/cu.mm respectively for the group T_3 were 4.7, 4.6 and 5.4 millions/cu.mm respectively and for the group T_4 were 5.5, 4.3 and 5.5 millions/cu.mm respectively. The WBC count before, during and after anaesthesia were 12560, 6300 and 9900/cu.mm respectively for the group C, 10460, 7420 and 10020/cu.mm respectively for the group T_1, 9480, 8270 and 8690/cu.mm respectively for the group T_2, 11420, 9810 and 11020/cu.mm respectively for group T_3 and 14830, 12870 and 12940/cu.mm respectively for the group T_4. The values for ESR for the 5 groups before anaesthesia were 1.2, 6.6, 2.0, 4.8 and 10 mm/hr respectively, during anaesthesia were 2.0, 5.8, 1.0, 5.0 and 9.0 mm/hr respectively and after anaesthesia were 2.0, 8.8, 2.0, 5.0 and 10.0 mm/hr respectively. The corresponding values for PCV were 42, 41, 40, 49 and 46 per cent respectively for the five groups before anaesthesia, 35, 42, 39, 47 and 45 per cent respectively during anaesthesia and 43, 43, 39, 47 and 49 per cent respectively after anaesthesia. The values for Hb for the five groups before anaesthesia were 9.2, 8.8, 8.6, 7.5 and 8.0 g/dl respectively during anaesthesia were 7.4,

9.0, 7.8, 7.4 and 7.8 g/dl respectively and after anaesthesia were 8.6, 8.8,8.0, 7.4 and 7.8 g/dl respectively. On statistical analysis only the RBC count was found to show a significant decrease during anaesthesia and this was present in all the groups. The mean values for PCV, ESR, Hb and WBC count showed no significant difference before, during and after anaesthesia. Similarly the DC also showed a more or less uniform picture during anaesthesia.

Table 2. Effect of Tiletamine - Zolazepam - Xylazine administration on the anaesthetic Parameters in dogs. (Mean±SE)

n = 6 Time of injection of Zoletil is taken as '0'

Group	Time of recumbency (Sec.)	Disappearance of tail clamp reflex (min)	Disappearance of skin clamp reflex (min)	Time of regain of righting reflex (min)	Reappearance of tail clamp reflex (min)	Reappearance of skin clamp reflex (min)	Time of regain of sternal recumbency (min)	Time for standing (min)	Time for walking (min)
C	13.3 ±3.8	4.5 ±0.5	8.8 ±0.8	23.8 ±2.2	23.5 ±1.2	29.5 ±1.3	42.8 ±2.0	73.3 ±3.9	78.2 ±4.4
T_1	15.8 ±3.8	5.2 ±0.6	8.7 ±0.8	28.8 ±2.2	20.2 ±1.2	23.3 ±1.3	33.2 ±2.0	48.0 ±3.9	50.8 ±4.4
T_2	0.0 ±0.0	4.0 ±0.6	7.5 ±0.8	35.3 ±2.2	18.6 ±1.2	22.7 ±1.3	43.3 ±2.0	47.5 ±3.9	48.3 ±4.4
T_3	6.7 ±3.8	2.7 ±0.6	4.7 ±0.8	24.0 ±2.2	14.2 ±1.2	14.8 ±1.3	28.5 ±2.0	41.3 ±3.9	42.2 ±4.4
T_4	9.2 ±3.8	2.8 ±0.6	4.8 ±0.8	24.8 ±2.2	15.7 ±1.2	16.7 ±1.3	29.8 ±2.0	39.5 ±3.9	40.8 ±4.4

C - Tiletamine-zolazepam (5 mg/kg)

T_1 - Tiletamine-zolazepam (2.5 mg/kg) ± Xylazine (0.5 mg/kg)

T_2 - Tiletamine-zolazepam (1.25 mg/kg) ± Xylazine (1 mg/kg)

T_3 - Tiletamine-zolazepam (1.25 mg/kg) ± Xylazine (1 mg/kg) ± aminophylline (20 mg/kg)

T_4 - Tiletamine-zolazepam (1.25 mg/kg) ± Xylazine (1 mg/kg) aminophylline (40 mg/kg)

Table 3. Effect of Tiletamine - Zolazepam - Xylazine administration on the anaesthetic parameters in dogs (mean).

n = 6 — Time of injection of Zoletil is taken as '0'

Group	Time from injection to beginning of tail clamp anaesthesia (min)	Induction time (min)	Duration of skin clamp anaesthesia (min)	Duration of tail clamp anaesthesia (min)	Recovery time (min)	Time from sternal recumbency to standing (min)	Duration of Zoletil effect (min)	Time of reappearance of ear twitch reflex (min.)	Time of reappearance of pedal reflex (min.)
C	4.5	8.8	20.5	19.0	13.5	73.3	78.2	30.8	-
T_1	5.2	8.7	14.0	15.0	10.0	48.0	50.8	23.4	21.5
T_2	4.0	9.2	15.2	14.7	20.7	47.5	48.2	29.8	28.5
T_3	2.7	2.8	10.1	11.5	13.7	41.3	42.2	21.6	20.5
T_4	2.8	4.8	11.9	12.8	13.1	39.5	40.8	22.7	19.0

Table 4. Effect of Tiletamine - Zolazepam - Xylazine administration on the rectal temperature in dogs (mean ± SE).

n = 6 Time of injection of Zoletil is taken as '0'

Group	Time in minutes									
	0	5	10	15	20	30	45	60	90	120
C	101.1 ±0.3	101.5 ±0.3	102.5 ±0.3	101.6 ±0.3	101.3 ±0.3	100.9 ±0.3	100.9 ±0.3	101.6 ±0.5	102.0 ±0.5	101.7 ±0.3
T_1	102.2 ±0.3	101.9 ±0.3	101.8 ±0.3	101.4 ±0.3	101.3 ±0.3	101.2 ±0.3	101.3 ±0.3	101.6 ±0.5	101.4 ±0.5	101.4 ±0.3
T_2	101.9 ±0.3	101.8 ±0.3	101.8 ±0.3	101.5 ±0.3	101.4 ±0.3	101.2 ±0.3	101.2 ±0.3	101.2 ±0.5	101.5 ±0.5	101.3 ±0.3
T_3	101.4 ±0.3	101.3 ±0.3	100.7 ±0.3	100.7 ±0.3	100.6 ±0.3	100.6 ±0.3	100.8 ±0.3	101.4 ±0.5	101.6 ±0.5	101.6 ±0.3
T_4	101.3 ±0.3	101.1 ±0.3	100.9 ±0.3	100.6 ±0.3	100.7 ±0.3	100.9 ±0.3	100.9 ±0.3	101.1 ±0.5	101.2 ±0.5	101.5 ±0.3

Table 5. Effect of Tiletamine - Zolazepam - Xylazine administration on the pulse rate in dogs (mean ± SE)

n = 6 — Time of injection of Zoletil is taken as '0'

Group	Time in minutes									
	0	5	10	15	20	30	45	60	90 ——	120
C	21.0 ±1.8	36.0 ±2.5	36.0 ±3.4	43.0 ±2.1	35.0 ±2.1	27.0 ±2.2	30.0 ±2.3	26.0 ±2.2	31.0 ±2.5	24.0 ±1.9
T_2	18.0 ±1.8	26.0 ±2.5	28.0 ±3.4	32.0 ±2.1	30.0 ±2.1	27.0 ±2.2	27.0 ±2.3	24.0 ±2.2	22.0 ±2.5	20.0 ±1.9
T_3	19.0 ±1.8	30.0 ±2.5	34.0 ±3.4	36.0 ±2.1	36.0 ±2.1	28.0 ±2.2	25.0 ±2.3	23.0 ±2.2	21.0 ±2.5	21.0 ±1.9
T_3	20.0 ±1.8	29.0 ±2.5	34.0 ±3.4	32.0 ±2.1	31.0 ±2.1	30.0 ±2.2	27.0 ±2.3	24.0 ±2.2	22.0 ±2.5	20.0 ±1.9
T_4	19.0 ±1.8	28.0 ±2.5	32.0 ±3.4	34.0 ±2.1	33.0 ±2.1	30.0 ±2.2	29.0 ±2.3	26.0 ±2.2	24.0 ±2.5	24.0 ±1.9

Table 6. Effect of Tiletamine - Zolazepam - Xylazine administration on the respiration rate in dogs (mean ± SE).

n = 6 Time of injection of Zoletil is taken as '0'

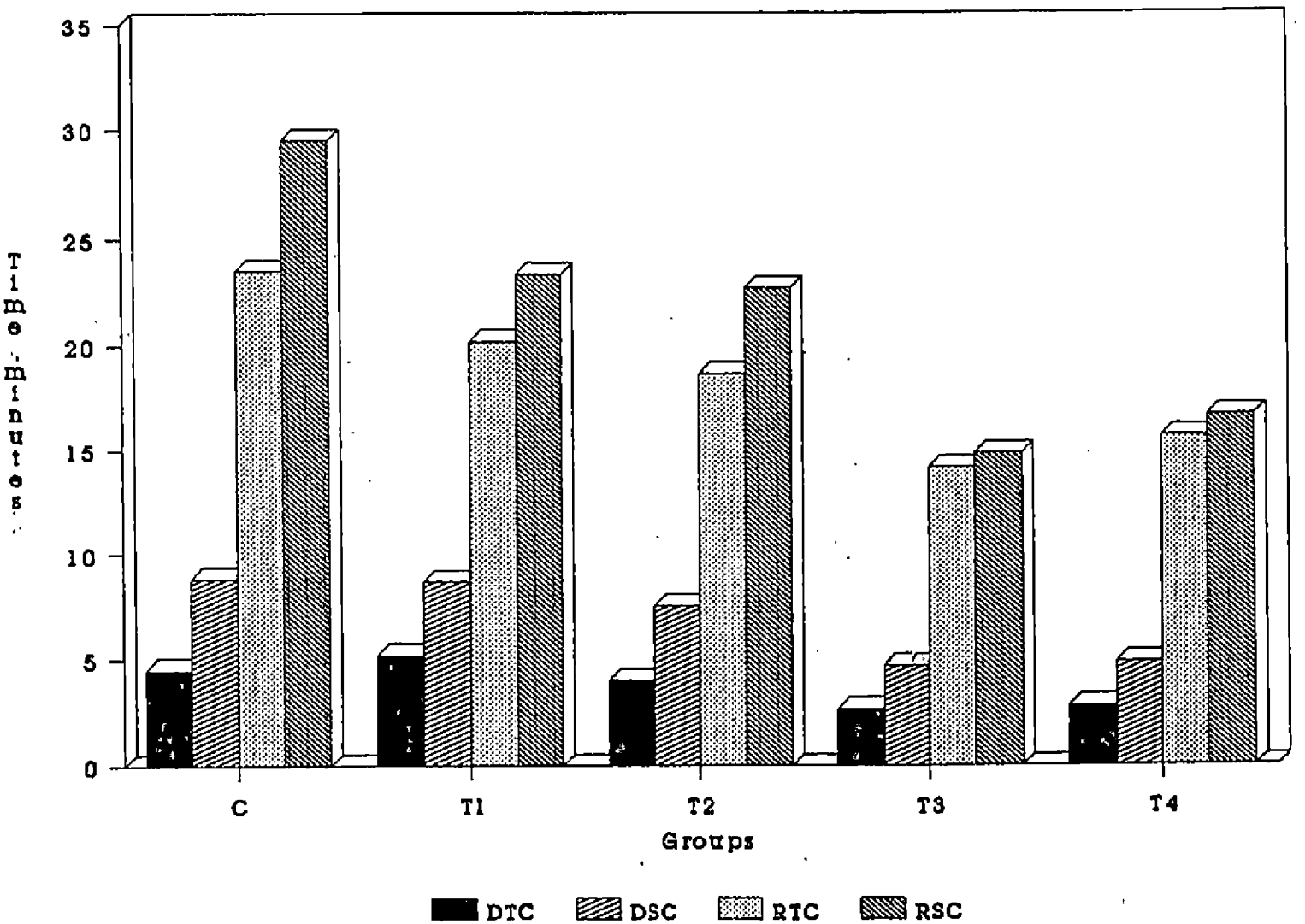
Group	Time in minutes									
	0	5	10	15	20	30	45	60	90	120
C	12.0 ±2.0	8.0 ±0.7	10.0 ±0.7	9.0 ±0.6	10.0 ±0.8	9.0 ±0.9	9.0 ±1.3	12.0 ±1.3	25.0 ±2.6	33.0 ±3.8
T_1	11.0 ±2.0	4.0 ±0.7	3.0 ±0.7	3.0 ±0.6	4.0 ±0.8	7.0 ±0.9	9.0 ±1.3	10.0 ±1.3	13.0 ±2.6	15.0 ±3.8
T_2	13.0 ±2.0	3.0 ±0.7	3.0 ±0.7	4.0 ±0.6	5.0 ±0.8	6.0 ±0.9	5.0 ±1.3	7.0 ±1.3	13.0 ±2.6	18.0 ±3.8
T_3	8.0 ±2.0	4.0 ±0.7	4.0 ±0.7	4.0 ±0.6	5.0 ±0.8	6.0 ±0.9	7.0 ±1.3	7.0 ±1.3	9.0 ±2.6	9.0 ±3.8
T_4	8.0 ±2.0	3.0 ±0.7	3.0 ±0.7	4.0 ±0.6	4.0 ±0.8	6.0 ±0.9	7.0 ±1.3	8.0 ±1.3	8.0 ±2.6	9.0 ±3.8

Table 7. Effect of Tiletamine - Zolazepam - Xylazine administration on the haematological parameters (mean) in dogs.

n = 6

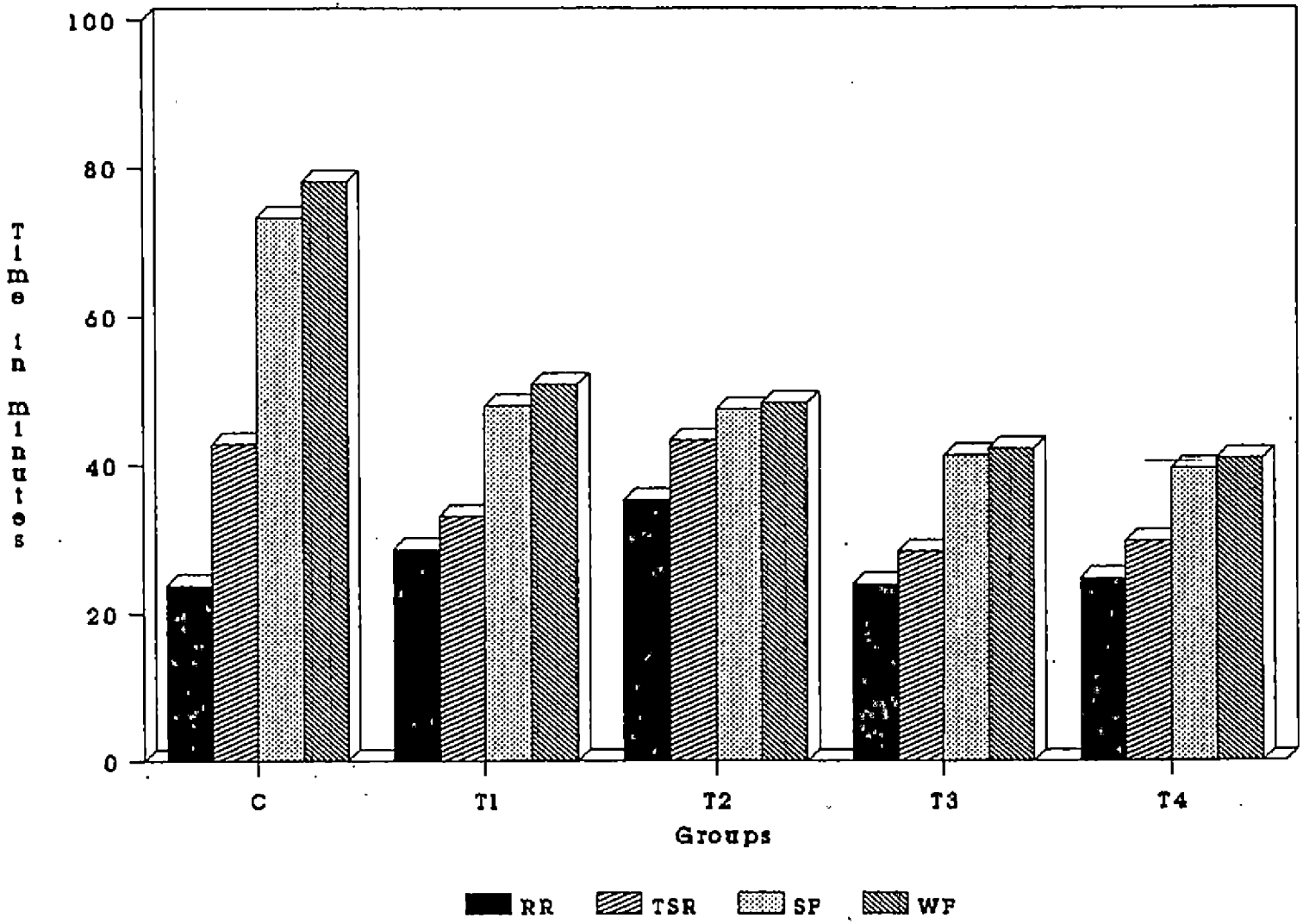
		RBC/ cu.mm	WBC/ cu.mm	ESR mm/h	PCV %	Hb g/dl	Neu %	Lym %	Bas %	Eos %	Mono %
	C	5970000	12560	1.2	42	9.2	68	27	1	4	-
	T_1	5650000	10460	6.6	41	8.8	67	28	-	4	1
BEFORE	T_2	5510000	9480	2.0	40	8.6	68	29	1	2	-
	T_3	4700000	11420	4.8	49	7.5	68	28	-	3	1
	T_4	5580000	14830	10.0	46	8.0	70	27	1	2	-
	C	4430000	6300	2.0	35	7.4	71	25	1	3	-
	T_1	5010000	7420	5.8	42	9.0	70	25	1	4	-
DURING	T_2	4390000	8270	1.0	39	7.8	68	28	1	3	-
	T_3	4680000	9810	5.0	47	7.4	66	29	-	4	1
	T_4	4300000	12870	9.0	45	7.8	67	30	1	3	-
	C	6920000	9900	2.0	43	8.6	70	24	1	5	-
	T_1	5530000	10020	8.8	43	8.8	68	24	1	4	-
AFTER	T_2	5060000	8690	2.0	39	8.0	68	28	-	3	1
	T_3	5470000	11020	5.0	47	7.4	65	30	-	4	1
	T_4	5500000	12940	10.0	49	7.8	68	28	1	3	-

FIG.1 EFFECT OF TILETAMINE-ZOLAZEPAM-XYLAZINE ADMINISTRATION ON THE ANAESTHETIC PARAMETERS IN DOGS.



DTC-Disappearance of tail clamp reflex DSC-Disappearance of skin clamp reflex
RTC-Reappearance of tail clamp reflex DSC-Reappearance of skin clamp reflex

FIG.2 EFFECT OF TILETAMINE-ZOLAZEPAM-XYLAZINE ADMINISTRATION ON THE ANAESTHETIC PARAMETERS IN DOGS



RR-Regaining of righting reflex
TSR-Regaining of sternal recumbency
SF-Standing up first
WF -Walking first

FIG.3 EFFECT OF TILETAMINE-ZOLAZEPAM-XYLAZINE ADMINISTRATION ON THE RECTAL TEMPERATURE IN DOGS

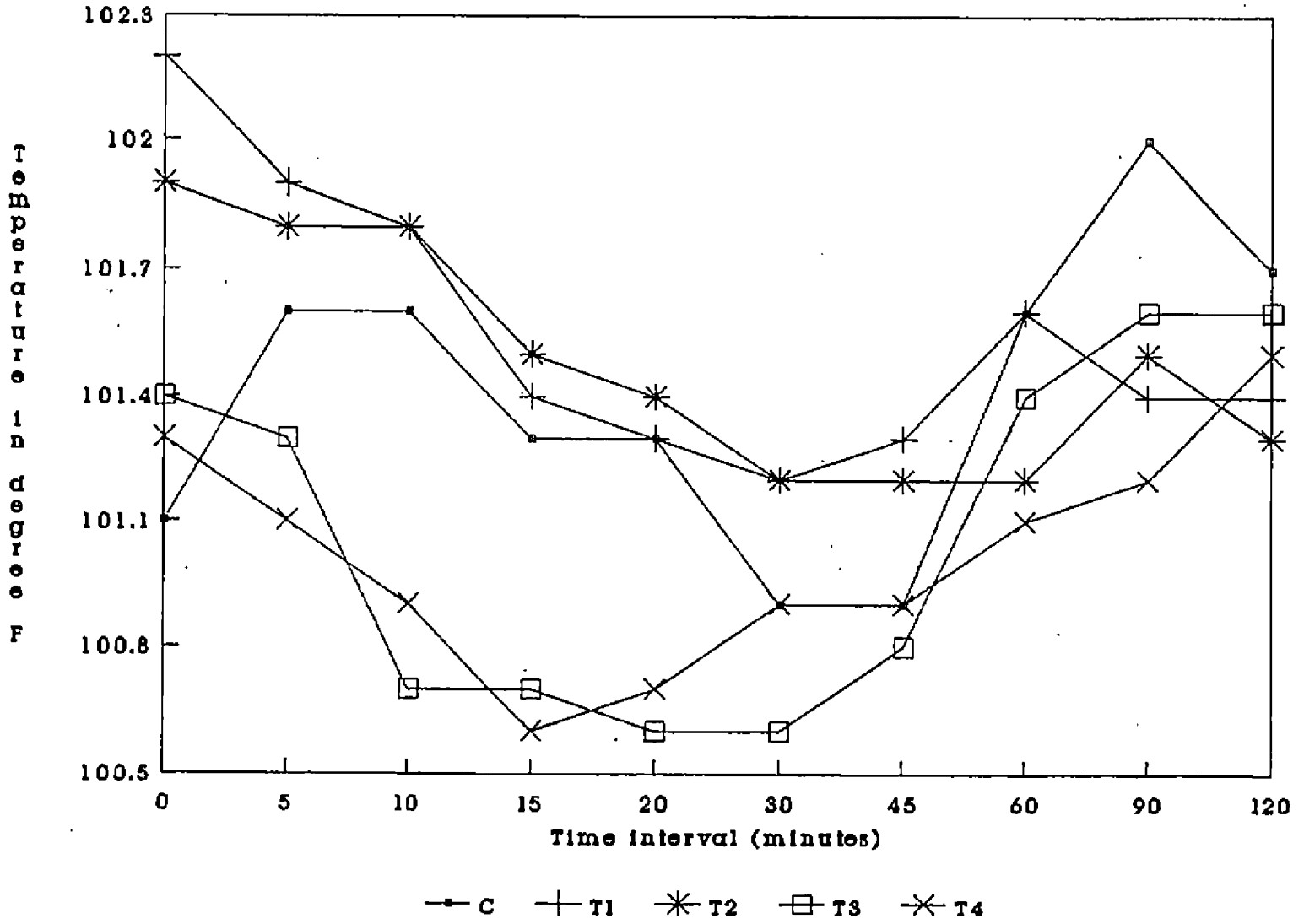


FIG.4 EFFECT OF TILETAMINE-ZOLAZEPAM-XYLAZINE ADMINISTRATION ON THE PULSE RATE IN DOGS

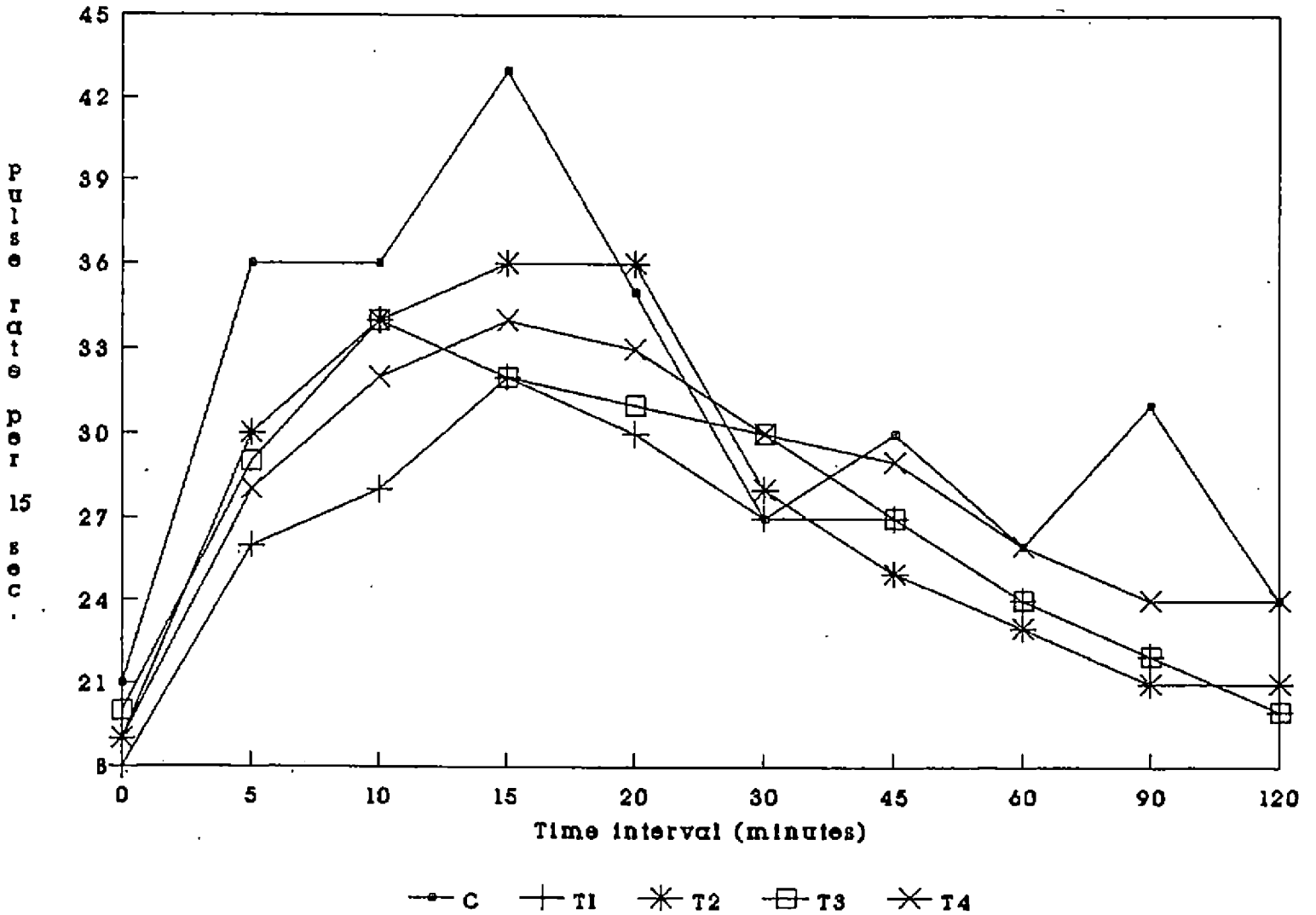
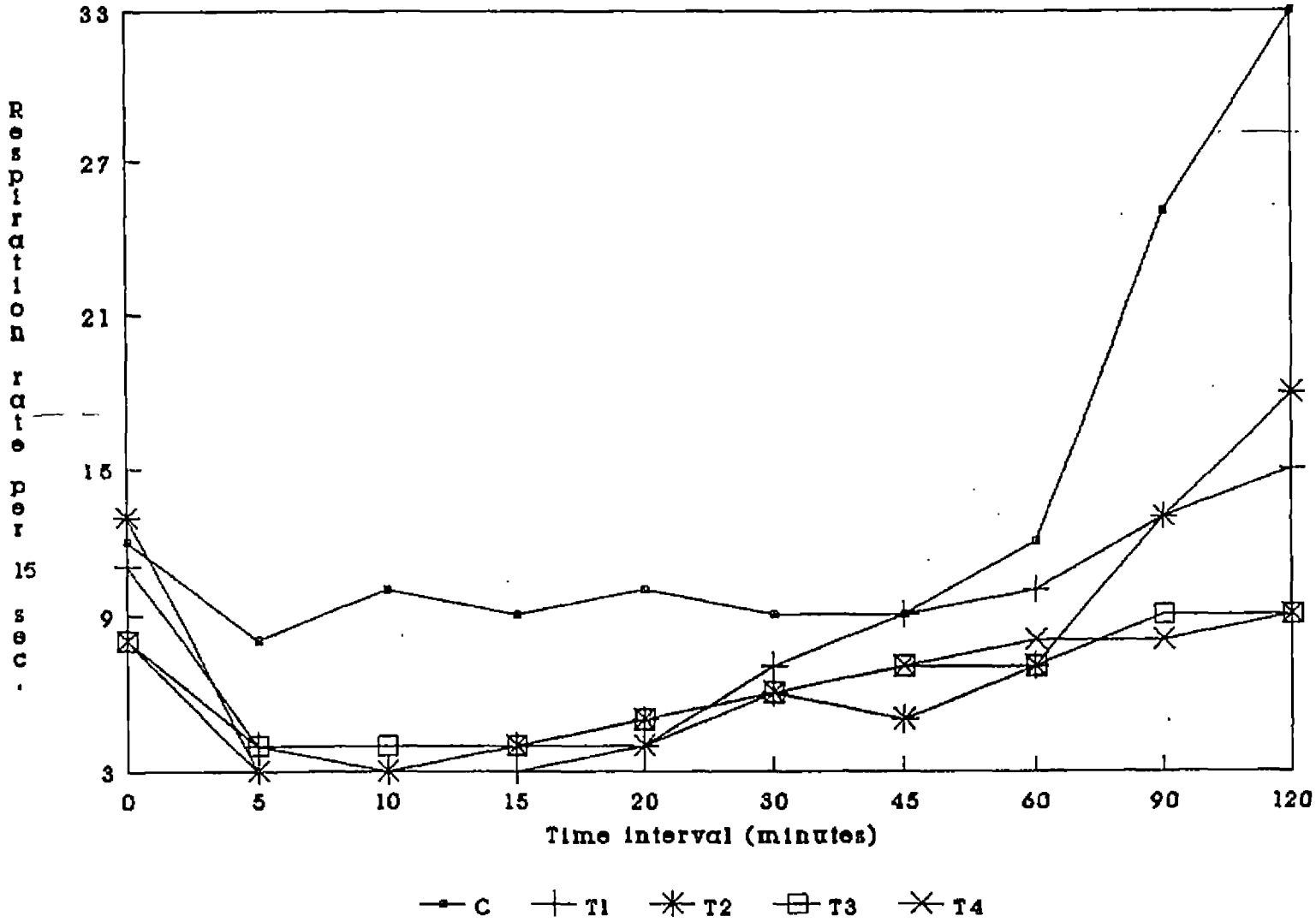


FIG.5 EFFECT OF TILETAMINE-ZOLAZEPAM-XYLAZINE ADMINISTRATION ON RESPIRATION RATE IN DOGS



Discussion

DISCUSSION

The objectives of the present study were (1) to test the synergistic effect of xylazine with tiletamine zolazepam anaesthesia (2) to test the efficacy of aminophylline as an antagonist to tiletamine-zolazepam-xylazine anaesthesia. The results of the study are discussed accordingly in 2 parts. The first part of this chapter discusses the results of the trials conducted to test the synergistic effect of xylazine on tiletamine zolazepam anaesthesia. The second part discusses the action of aminophylline, an adenosine receptor blocker and phosphodiesterase inhibitor (Gilman et al., 1991) as a reversing agent for tiletamine-zolazepam xylazine anaesthesia. For ease of discussion, the results are therefore analysed in two parts - the first part dealing with the comparison of the results of the treatments C, T_1 and T_2 and the second part giving the comparison of the results of the treatments T_2, T_3 and T_4.

The dissociative anaesthetics, when used alone, are unable to induce and maintain satisfactory anaesthesia (narcosis muscle relaxation and analgesia). But when combined with drugs that complement their effects, they may be used safely to induce balanced anaesthesia. Some alpha-2 agonists have been shown to possess actions that complement the dissociative anaesthetics (Thurmon et al., 1989).

Xylazine, an alpha-2 adrenoceptor agonist, was found to produce sedation, muscle relaxation and analgesia in dogs (Lacuata and Flores, 1972). Xylazine has been used extensively in combination with tiletamine, barbiturates and guaifenesin, because of its superior sedative, analgesic and muscle-relaxing properties. The combination of xylazine and ketamine has been used extensively to anaesthetize dogs and cats (Navorro and Friedman, 1975; Amend et al., 1972; Haskins et al., 1986 and Duke et al., 1988). Therefore, when xylazine is combined with tiletamine-zolazepam, it should improve the muscle-relaxation and analgesia, while decreasing the total dose of the combination required for surgical anaesthesia.

In the present study, the time of recumbency showed no significant difference between the groups C, T_1 and T_2. This showed that xylazine premedication, 15 minutes prior to anaesthesia, did not affect the time of recumbency. The same observation was reported by Thurmon et al. in swine (1988) and in calves (1989) and also by Abrahamsen et al. in horses (1991).

The two methods of nociceptive stimuli used viz. skin clamp and tail clamp application, simulated surgical procedures involving the skin, the sub-cutis, bone,

significantly greater values for the control group and smallest values for T_2. This also suggests that xylazine has no significant effect on the duration of Zoletil anaesthesia.

The duration of skin clamp anaesthesia was found to be more for the group C and lesser for the group T_2. The duration of tail clamp anaesthesia also presented a similar picture. This also suggests that duration of anaesthesia is more influenced by tiletamine-zolazepam than by xylazine. No significant difference could be noted for the mean induction time and recovery time between the three groups.

Protective reflexes such as the coughing reflex, swallowing reflex, the corneal reflex and the pedal reflex are usually maintained in tiletamine-zolazepam anaesthesia (Short, 1987). In the present study also, these reflexes remained active throughout anaesthesia in the control group. The greater concentration of xylazine might have contributed to the disappearance and subsequent reappearance of the pedal and ear twitch reflexes in the T_2 group.

Frequent whining, paddling and occasional head and neck rocking were the most noticeable side effects during recovery. These were absent in groups T_1 and T_2. All the

three effects varied in frequency from occasional to continuous. Paddling was manifested by continuous or semi continuous movements of all four limbs. In all cases, these side effects stopped once the dogs attained sternal recumbency.

Pharmacological studies on tiletamine and zolezepam in dogs have revealed that the plasma half-life of zolazepam is less than 1 hour, whereas that of tiletamine is 1.2 hours (Donaldson et al., 1989). The progressive increase in muscle activity as evidenced by the paddling and the head and neck rocking reflects this variation in the plasma half-lives of the 2 components. Another contributing factor may be the inhibition of the motor reflexes at the spinal cord level and the altered postural tone and muscle co-ordination at the cerebellar and striatal level by the zolazepam (Donaldson et al., 1989). This may cause an increasing gradient of muscle-relaxation from head to tail, thus substantiating for the increased rigidity of the head and neck muscles and the characteristic rocking seen initially during the recovery phase.

A significant reduction in rectal temperature was noticed in all the 3 groups at 30 minutes post anaesthesia, which may be attributed to the general sedation, CNS

depression, reduced metabolic rate and inhibition of skeletal muscle movements during anaesthesia. A similar hypothermia was reported during xylazine-ketamine anaesthesia by Kral et al. (1974) in cats. Short (1987) has also reported that the tiletamine-zolazepam combination caused a transient decrease in rectal temperature in dogs and cats. There was no statistically significant difference in the hypothermia produced between the three groups.

The change in pulse rate was biphasic, first increasing and then decreasing. This response agrees with that in calves where Telazol-xylazine combination was administered (Thurmon et al., 1989). The initial increase in pulse rate in the present study appears to be in response to the tiletamine-zolezepam drug combination. The pulse rate increased significantly in the control group when compared to T_1 and T_2 in 15 minutes time, perhaps due to the larger dose of tiletamine zolazepam combination administered. Tiletamine induces tachycardia in unanaesthetized dogs, whereas zolazepam has little or no effect on the cardiovascular performances and heart-rate. So, xylazine appears mostly responsible for the pulse rate decrease that followed the initial increase. Haskins et al. (1985) observed an increase in pulse rate during ketamine

anaesthesia which was attributed to be due to the centrally mediated generalised increase in sympathetic tone.

Changes in the respiratory rate were also biphasic (first decreasing and then increasing). These changes in the respiratory rate are unlike those observed in pigs (Thurmon et al. 1988) but similar to those in horses (Hubbel et al., 1989). The exact cause for this biphasic response is unknown though xylazine has been reported to decrease the rate of breathing (Bollwahn et al. 1970) possibly by a direct inhibitory action on the medullary centre. For the first 5 to 30 minutes during anaesthesia, the decrease in respiratory rate had been significantly greater for the group T_2 when compared to the control, which might be due to a higher dose of xylazine.

The haematological picture showed no significant difference between the groups before during and after anaesthesia, except for the RBC count. The RBC count showed a transitory fall during anaesthesia which might be attributed to the pooling of erythrocytes in the spleen. Kumar et al. (1974) has reported that the minor changes in the RBC count during ketamine anaesthesia might be associated with the stress and spleenic engorgement during anaesthesia.

From the aforesaid discussion, it can be said that the combination of tiletamine-zolazepam (1.25 mg/kg) and xylazine (1 mg/kg) appears to induce safe, short term satisfactory anaesthesia in dogs.

In the second part of the experiment, reversal of the tiletamine-zolazepam (1.25 mg/kg) and Xylazine (1 mg/kg) anaesthesia using 2 doses of aminophylline (20 mg/kg and 40 mg/kg respectively) was studied.

The time of recumbency, the induction time and the time of appearance of both skin clamp and tail clamp anaesthesia showed no significant difference between the 3 groups because the anaesthetic schedule was the same for all.

The time of disappearance of tail clamp anaesthesia showed significant difference between T_2 and T_3, but not between T_3 and T_4. The significantly shorter time of disappearance of tail clamp anaesthesia for T_3 shows the antagonistic property of the lower dose of aminophylline tested against tiletamine-zolazepam-xylazine anaesthesia. The time of disappearance of skin clamp anaesthesia and the time of appearance of righting reflex also showed significant variation between the groups T_2 and T_3 and also

between T_2 and T_4. But the values for these two showed no significant difference between T_3 and T_4. The time for regain of sternal recumbency was also significantly different between the groups T_2 and T_3 and also between T_2 and T_4. All these proved that aminophylline could effectively reverse the anaesthesia produced by tiletamine-zolazepam-xylazine combination.

Aminophylline is an adenosine receptor blocker and a phosphodiesterase inhibitor which acts by causing an accumulation of cAMP and by competitively antagonising adenosine at the receptor level. In contrast, xylazine, an alpha-2 agonist primarily acts by causing an inhibition of adenylyl cyclase, the enzyme responsible for the synthesis of cAMP. The inhibition of secretion of catecholamines by xylazine can also be effectively antagonised by aminophylline which can augment the release of catacholamines from nerve terminals and reduce the uptake and/or metabolism of catecholamines in non-neural tissues (Gilman et al. 1991).

Aminophylline was earlier tried by Hatch et al. (1988) as an antagonist to Telazol overdose in dogs. They revealed that the drug caused a lightening of anaesthesia, as evidenced by movements, licking, blinking and sharpened pedal, palpebral and skin twitch reflexes. The rapid

reversal of tiletamine-zolazepam xylazine anaesthesia might be due to the antagonizing property of aminophylline against xylazine and a lower dose to tiletamine-zolezepam.

Aminophylline did not have much effect on the time for standing and walking. Although aminophylline did not hasten walking this could be an advantage as suggested by Hatch et al. (1988). Dogs attempting to stand prematurely may fall repeatedly and disrupt surgical or orthopaedic repairs or cause other injuries or accidents.

The duration of both skin clamp anaesthesia and tail clamp anaesthesia, the induction time and the recovery time were significantly shorter for T_3 and T_4 than those obtained for T_2. These also prove that aminophylline both at 20 mg/kg and 40 mg/kg dose rate intravenously is effective as a reversing agent for tiletamine-zolazepam-xylazine anaesthesia and that there is no additional advantage by increasing the dose of aminophylline from 20 to 40 mg/kg body weight.

The body temperature variation showed a similar pattern for the groups T_2, T_3 and T_4 during the entire duration of anaesthesia except at 10 minutes time. At 10 minutes, the decrease in body temperature was found to be significantly

greater for T_3 and T_4 when compared to T_2. Though the exact cause for this phenomenon is not fully understood, the adenosine receptor blocking property of aminophylline can be substantiated to be responsible for this effect. Since the temperature does not fall beyond clinically acceptable limits, this decrease is not clinically important.

The pulse rate and respiration rate also did not show significant difference between the groups T_2, T_3 and T_4 during the entire 2 hours of monitoring. The hemogram also presented a similar picture with the 3 groups before, during and after anaesthesia.

Based on the results of the experimentation, it could be concluded that, the combination of tiletamine-zolazepam (1.25 mg/kg body weight intravenous) and xylazine (1 mg/kg body weight intramuscular) is effective in producing satisfactory anaesthesia of short duration in dogs. The study also pointed out that aminophylline at a dose rate of 20 mg/kg intravenously can adequately reverse the anaesthesia produced by the drug combination.

Summary and Conclusion

SUMMARY AND CONCLUSION

The study was conducted with the following objectives:

1. To find out the synergistic effect of xylazine with tiletamine-zolezepam anaesthesia

2. To study the efficacy of aminophylline as a reversing agent in tiletamine-zolezepam-xylazine anaesthesia.

The study was conducted in 30 adult healthy dogs divided into five batches of six each. The first group of animals (C) received tiletamine-zolezepam at a dose rate of 5 mg/kg I/V. The second group of animals (T_1) received xylazine at a dose rate of 0.5 mg/kg I/M and 15 minutes later tiletamine-zolezepam at a dose rate of 2.5 mg/kg body weight I/V. The third group of animals (T_2) received xylazine at the rate of 1 mg/kg I/M and 15 minutes later tiletamine-zolazepam at a dose rate of 1.25 mg/kg I/V. The treatment schedule that resulted in greater duration of anaesthesia was chosen for studying the reversal effect of aminophylline in the subsequent two groups. Since group T_2 was found to produce anaesthesia of larger duration, the treatment schedule of that was adopted for subsequent studies. The fourth group of animals (T_3) received the anaesthetic schedule as in T_2. In the middle of anaesthesia ie. after 8 minutes of appearance of skin clamp anaesthesia, the animals were given aminophylline at a dose rate of 20 mg/kg I/V. In

the fifth group of animals (T_4) the same treatment schedule as in T_2 was adopted and at the middle of anaesthesia, aminophylline was administered I/V at a dose rate of 40 mg/kg.

The anaesthetic parameters like the time of recumbency, time of appearance and disappearance of skin clamp anaesthesia and tail clamp anaesthesia, time of regaining of righting reflex, time of regaining of sternal recumbency and the time for standing and walking were recorded for all treatments. The rectal temperature, pulse rate and respiration rate were recorded at 0, 5, 10, 15, 20, 30, 45, 60, 90 and 120 minutes during anaesthesia. The haemogram was also studied before during and after anaesthesia for all treatments.

The mean time of recumbency for the groups C, T_1, T_2, T_3 and T_4 were 13.3, 15.8, 0, 6.7 and 9.2 seconds respectively. There was no significant difference in these values between the groups. Similarly, the mean time of disappearance of tail clamp reflex and skin clamp reflex also showed no significant difference between the different groups.

The time of disappearance of tail clamp anaesthesia for the different groups C, T_1, T_2, T_3 and T_4 were 23.5, 20.2,

18.7, 14.2 and 15.7 minutes respectively. Statistical analysis proved that significant difference existed between the groups C and T_2 and also between T_2 and T_3 in the time of appearance of tail clamp reflex.

The end of skin clamp anaesthesia was noted at 29.5, 23.3, 22.7, 14.8 and 16.7 minutes respectively for the five groups after the administration of Zoletil. These values were found to be significantly different between the groups C and T_2 and also between T_2 and T_3 and T_4. The time of regain of righting reflex and the time for sternal recumbency also showed significant difference between the groups C and T_2 and also between T_2 and T_3 and T_4. The mean values for the time of regain of righting reflex were 23.8, 28.8, 35.3, 24 and 24.8 minutes respectively, and for the time of sternal recumbency were 29.5, 23.3, 22.7, 14.8 and 16.7 minutes respectively.

The mean time for standing and walking showed significant difference only between the control group (73.3 and 78.2 minutes respectively) and T_2 (47.5 and 48.3 minutes respectively. There was no significant difference between T_2, T_3 and T_4 for these parameters.

The duration of skin clamp anaesthesia, the duration of tail clamp anaesthesia and the recovery time were significantly shorter for the group T_3 when compared to T_2.

The most noticeable behavioural characteristics were rhythmic head and neck rocking, paddling and whining during the recovery time and these were present only in the control group.

The rectal temperature showed a similar pattern of variation in all the groups ie. a progressive decrease of about 0.8-2°F upto 30 minutes post-anaesthesia and then an increase to near pre-anaesthestic values by about 90 minutes time. Statistical analysis revealed no significant difference between the different groups except at 10 minutes time, when the decrease in temperature was found to be greater for T_3 and T_4 when compared to T_2.

The pulse rate also showed a uniform trend in all the groups with a progressive increase from a mean baseline value of 19/15 sec. to about 35/15 sec. in 15 minutes time and then a gradual fall to a mean value of 22/15 sec in 120 minutes time. The increase in pulse rate varied significantly only at 15 minutes time and the increase was greater for the group C when compared to T_2.

The respiratory rate decreased to a mean value of 4/15 sec. in 5 minutes post-anaesthesia and later increased gradually to a mean value of 17/15 sec. in 120 minutes time in all the groups, except the control group in which there

was not much variation in the respiratory rate throughout anaesthesia. There was significant difference between the groups C and T_2 only, from 5 to 30 minutes during anaesthesia, with the decrease in the respiratory rate being greater with the group T_2 when compared to C.

The total WBC count, ESR, PCV, Hb and the differential count showed no significant difference between the groups before, during and after anaesthesia. Only the RBC count showed a significant decrease during anaesthesia in all the groups.

From the results of the experiments, it could be concluded that (1) the combination of xylazine (1 mg/kg, intramuscular) and tiletamine-zolazepam (1.25 mg/kg, intravenous) could produce satisfactory, short-term anaesthesia in dogs. (2) aminophylline at a dose rate of 20 mg/kg intravenously could effectively antagonize the anaesthesia produced by the tiletamine-zolazepam-xylazine combination. Therefore this anaesthetic regimen can be well-suggested for surgical practice in canines.

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TILETAMINE-ZOLAZEPAM ANAESTHESIA WITH XYLAZINE PREMEDICATION AND REVERSAL WITH AMINOPHYLLINE IN DOGS

By

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ABSTRACT OF A THESIS

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ABSTRACT

The experiment was conducted to find out the synergistic effect of xylazine with tiletamine-zolazepam anaesthesia and to study the reversing action of aminophylline in tiletamine-zolazepam-xylazine anaesthesia. The study was conducted in 5 batches of 6 dogs each. The first group of animals (C) received tiletamine-zolazepam at the rate of 5 mg/kg I/V. The second group (T_1) received xylazine (0.5 mg/kg I/M) and 15 minutes later, tiletamine-zolazepam (2.5 mg/kg I/V). The third group (T_2) received xylazine (1 mg/kg I/M) and 15 minutes later, tiletamine-zolazepam (1.25 mg/kg I/V) The treatment schedule that resulted in a greater duration of anaesthesia ie, T_2, was chosen for studies in the subsequent groups. The fourth (T_3) and fifth (T_4) group of animals received the anaesthesia scheduled as in T_2, and in the middle of anaesthesia ie. after 8 minutes, the animals were given aminophylline intravenously at the dose rate of 20 mg/kg and 40 mg/kg respectively.

The anaesthetic parameters like the time of recumbency, time of appearance and disappearance of skin clamp and tail clamp anaesthesia, time of regaining of righting reflex and sternal recumbency, and the time for standing and walking were recorded for all treatments. The rectal temperature, pulse rate and respiration rate were recorded at 0, 5, 10,

15, 20, 30, 45, 60, 90, and 120 minutes after administration of anaesthetic. The haemogram was also studied before, during and after anaesthesia.

All the animals came to recumbency after the injection of tiletamine-zolazepam within a mean time of 10 seconds. The time of recumbency and the time of appearance of tail clamp and skin clamp anaesthesia showed no significant difference between the different groups. The time of disappearance of tail clamp anaesthesia for the group C, T_1 and T_2 were 23.5, 20.2 and 18.6 minutes and for T_3 and T_4 were 14.2 and 15.7 minutes respectively. Time of disappearance of skin clamp anaesthesia for the groups C, T_1, and T_2 were 29.5, 23.3 and 22.7 minutes and for the groups T_3 and T_4 were 14.8 and 16.7 minutes respectively. The time of regaining of righting reflex for the groups C, T_1 and T_2 were 23.8, 28.8 and 35.3 minutes and for T_3 and T_4 were 24 and 24.8 minutes respectively. The time of sternal recumbency were 42.8, 33.2 and 43.3 minutes for the groups C, T_1 and T_2 and 28.5 and 29.8 minutes for T_3 and T_4 respectively. All these values showed significant difference between C and T_2 and also between T_2 and T_3 and T_4. The mean time for standing and walking showed significant difference only between the control group (73.3 and 78.2 minutes respectively) and T_2 (47.5 and 48.3 minutes respectively), but not between T_2, T_3 and T_4.

The duration of skin clamp anaesthesia, tail clamp anaesthesia and the recovery time were significantly shorter for the group T_3 when compared to T_2. The most noticeable behavioural characteristics during recovery were rhythmic head and neck rocking, whining and paddling and these were present only in the control group. There was no significant difference between the groups in the rectal temperature during anaesthesia except at 10 minutes time, when the decrease in temperature was greater for T_3 and T_4 when compared to T_2. There was no significant difference in the pulse rate also between the group throughout anaesthesia, with an exception only at 15 minutes when the increase in pulse rate was greater for C than for T_2. The decrease in respiratory rate was significantly greater for T_2 when compared to C from 5 to 30 minutes during anaesthesia. The haemogram showed no significant difference between the groups during anaesthesia.

From the results obtained, it could be concluded that

1) the combination of xylazine (1 mg/kg I/M) and tiletamine-zolazepam (1.25 mg/kg I/V) could be used to produce satisfactory, short-term anaesthesia in dogs and
2) aminophylline at a dose rate of 20 mg/kg I/V could be used to reverse anaesthesia produced by tiletamine-zolazepam-xylazine combination.