INFLUENCE OF BUPRENORPHINE, PENTAZOCINE AND XYLAZINE ANALGESIA ON KETAMINE ANAESTHESIA IN DOGS

By

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THESIS

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Dedicated to

my husband and parents

DECLARATION

I hereby declare that this thesis entitled "INFLUENCE OF BUPRENORPHINE, PENTAZOCINE AND XYLAZINE ANALGESIA ON KETAMINE ANAESTHESIA 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, fellowship or other similar title, of any other University or Society.

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Certified that this thesis entitled "INFLUENCE OF BUPRENORPHINE, PENTAZOCINE AND XYLAZINE ANALGESIA ON KETAMINE ANAESTHESIA IN DOGS" is a record of research work done independently by Smt. P.T.A. USHA 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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CHAPTER 1

Introduction

INTRODUCTION

Alleviation of pain is an ethical obligation accepted by all veterinarians. The experience of pain is subjective. Consequently it can never be proven that animal can feel pain. However, animals do display pain behaviour and it can be assessed from the behavioural responses of the animals. Difficulty in the definition of pain arises because pain is a subjective analysis of central nervous system. In animals pain has been defined as an aversive sensory and emotional experience that elicits protective motor actions, results in learned avoidance and modify species-specific traits of behaviour including social behaviour (Kitchell, 1987). Pain depends on activation of descrete set of receptors and neuronal pathway and is usually elicited by stimuli that are actually and potentially noxious. Pain relief must therefore be considered to be an essential part of veterinarian's treatment of animals.

Discovery of analgesics and anaesthetics made technical breakthrough in the medical management of pain. Experimental work on healthy laboratory animals, using techniques such as hot plate test and tail clip method can indicate the relative potencies of different analgesics. However the effect of analgesics on experimental pain often bear little relationship to their effect on clinical pain and if analgesics are to be used effectively to clinical pain, these must be assessed under clinical conditions (Taylor and Houlton, 1984).

A variety of drugs have been used for this purpose, from the earliest period of recorded history. Morphine derivatives were used in the earlier days as pain relievers. Later, quite a good number of synthetic drugs have been introduced.

Buprenorphine is a newly introduced drug, which is a derivative of thebaine, an opium alkaloid related to morphine and is a long acting analgesic with narcotic agonist and antagonist actions (Cowan, 1977a).

Pentazocine is a benzomorphan derivative having both agonistic and weak opioid antagonist activity. This produces CNS effects including analgesia, sedation and respiratory depression. Usually it is used as a post-operative analgesic in dogs (Taylor and Moulton, 1984).

Xylazine is a sedative, hypnotic, analgesic, narcotic and muscle relaxant and is also used in the chemical immobilization of wild animals.

The first part of the study involves the evaluation of analgesic potencies of the above three drugs in rats and mice.

Anaesthesia provides relief from pain and reflex responses and in the case of general anaesthesia there will be immobilization, relaxation and unconsciousness. The effective and safe general anaesthesia is essential for the efficient surgical manipulations. Inhalation anaesthesia was practised in the earlier days. This has got many disadvantages in veterinary practice. In an effort to produce effective and smooth general anaesthesia, intravenous anaesthetics like barbiturates were

introduced. In animals which were difficult for control and restraint, the intravenous anaesthesia becomes very difficult. This leads to the development of dissociative anaesthetics like ketamine, which can be administered intravenously as well as intramuscularly.

Ketamine is an ideal anaesthetic for children and in animal coming under the family felidae and subhuman primates. But satisfactory surgical anaesthesia will not be obtained with ketamine alone. The anaesthesia will not pass beyond stage II of the general anaesthesia. So ketamine should be combined with other drugs like analgesics or tranquillizers to get a satisfactory condition for handling the animals.

In this study different combinations of ketamine like ketamine-xylazine, ketamine-buprenorphine, ketamine-pentazocine were compared with ketamine anaesthesia in order to find out a better combination for practical use.

Ketamine-xylazine combinations are commonly used for chemical immobilisation of wild animals. Intramuscular administration of ketamine 15 mg/kg and xylazine 2 mg/kg produced anaesthesia for 30-40 min. (Haufman, 1976). But larger doses and repeated injections are frequently required to immobilize excited animals, however, recumbency can last for several hours (Fletcher, 1974). In such cases the reversal of anaesthesia may be useful.

The third part of the study involves the reversal of the above mentioned anaesthetic combinations using the alpha

blocking drug yohimbine. In earlier days morphine was used along with anaesthetics, for which appropriate antagonist is available. Since this is a narcotic drug, there will be difficulty in obtaining and using this due to narcotic regulations. This leads to the search for non-narcotic anaesthetic like ketamine. From the study of the mechanism of action, it was proved that the drug has got alpha receptor stimulating properties. So by blocking this alpha stimulant action, the effects of ketamine can be reversed. Alpha blocking drugs like yohimbine will be of great use in this regard. Since xylazine also acts mainly by stimulating alpha receptors, its effect can also be reversed by alpha blocking drugs. Alpha adrenergic antagonist yohimbine has been reported to be useful in the reversal of xylazine-ketamine anaesthesia in a wide variety of animals. Yohimbine has been reported to block xylazine induced CNS depression in mice (Hsu, 1981), in dog (Hsu, 1983), in cats (Hsu and Lu, 1984), reverse anaesthesia in cats (Hsu, et al., 1984), and in horses (Kitzman et al., 1984), reverse immobilization in elephants (Jacobson et al., 1985) and in Bengal Tigers (Seal et al., 1987).

The availability of yohimbine as an effective antagonist for the depressant effect of xylazine suggested the study of yohimbine's effects as an antagonist for xylazine and ketamine in dogs.

CHAPTER II

Review of Literature

REVIEW OF LITERATURE

II.1. Ketamine

Hoeppner et al. (1971) used ketamine in the following doses (mg/lb) in cats - 5 to 10 for restraints, 10 to 15 for light anaesthesia and 15 to 25 for deep anaesthesia. After intravenous injection, recumbency lasted for about 1.3 h. Standing time was 2.7 h. and total recovery in 13.5 h.

Deyoung et al. (1972) reported that the dissociative state produced by these agents in dog and cat is characterised by muscle rigidity and presence of many reflexes like swallowing, laryngeal and ocular, which are normally absent when conventional anaesthetic agents are used.

A dose of 10 mg/kg body weight of ketamine hydrochloride was injected intravenously into 36 dogs (Ploumis, 1976). The mean duration of deep surgical anaesthesia was 10 ± 4 min. The depth of anaesthesia could be judged not from usual reflexes but from reactions to induced pain. Satisfactory relaxation of the abdominal muscles was obtained. Average recovery time was 50 ± 7 min. Respiration rate increased after 4 min. and pressor response is also noticed.

Ketamine hydrochloride when used alone in 2 dogs showed severe muscular contractions and profuse salivation (Parsania et al., 1977). Hence promazine hydrochloride (Sparine) was used as premedicament. Twelve experimental animals and two clinical cases were given promazine hydrochloride at a dose

rate of 2.5 to 4 mg/kg intramuscularly, 15 min. prior to anaesthesia. Ketamine hydrochloride was given at a dose of 20-30 mg/kg intramuscularly or 10 mg/kg intravenously. Muscle relaxation was poor.

The cardiopulmonary consequences of ketamine (10 mg/kg) intravenously were studied by Haskins et al. (1965) in 10 mixed breed dogs. Arterial blood pressure, pulmonary artery pressure and central venous pressure were measured. All these parameters were transiently increased, immediately after ketamine administration. Arterial and venous blood were collected and pH, partial pressure of CO_2 (Pa CO_2), partial pressure of O_2 (Pa O_2), packed cell volume and haemoglobin were measured. Pa O_2 and pH were decreased. The Pa CO_2 increased significantly. Profuse salivation were also noticed.

Taylor et al. (1972) used ketamine in 10 ewes, 124 days pregnant. Anaesthesia was induced by a dose of 2 mg/kg followed by a drip infusion containing 2 mg/kg in 5 per cent dextrose given at a dose of 4 ml/min. Recovery took place within 10 to 15 min. of the end of the operation.

Thurmon et al. (1973) found that sheep became readily immobilized when given ketamine either i/m or i/v. Pretreatment with atropine sulphate prevented excessive salivation, increased degree of muscle relaxation and duration of analgesia. Dosages of 22 to 44 mg/kg body weight were adequate for short surgical and diagnostic procedures. Recovery was smooth and rapid.

Fuents and Tellez (1974) anaesthetised 10 cows, with ketamine 2 mg/kg body weight given by intravenous injection for induction and drip infusion of physiological saline solution of ketamine containing 2 mg/ml was used for maintenance at a rate of 10 ml/min. All animals were on feet, 30 min. after stopping the drip infusion.

Glenn et al. (1972) injected ketamine HCl intramuscularly in pit vipers, mambas, cobras and vipers and produced tranquil state or deep anaesthetic state depending on the dose used (22 to 132 mg/kg). The drug produced excellent anaesthesia for both brief and long surgical procedures.

The use of ketamine in 34 East African reptiles of 15 species was described by Cooper (1974). The drug produced effects ranging from tranquillization to deep anaesthesia. There was no apparent clinical or haematological side effects.

Effect of ketamine anaesthesia in buffalo calves was studied by Ramakrishna et al. (1981). Ten buffalo calves of $1\frac{1}{2}$ to 2 years of age were used. The drug was administered by rapid intravenous injection at a rate of 2 mg/kg body weight. Anaesthesia was maintained for one hour. There was no significant variation in rectal temperature but a slight increase in heart rate and respiration rate was noticed. All the animals showed marked salivation. Palpabral, corneal and laryngeal reflexes were present throughout. Pedal reflex was lost in 4 to 7 min. The eyes remained open and lateral nystagmus was often present. The haematological evaluation

showed slight decrease in total erythrocyte count, haemoglobin, packed cell volume and total leucocyte count. There was a significant neutrophilia with slight lymphopenia.

Fisher (1984) conducted field trial of ketamine anaesthesia in horse. Ketamine 2.2 mg/kg body weight was administered on 80 occasions to induce anaesthesia in 77 animals.

Pharmacokinetics of intravenously administered ketamine in horse was studied by Waterman et al. (1987). Metabolism and distribution of ketamine and its two major metabolites (norketamine and dehydronorketamine) were investigated in 10 horses. Following premedication with xylazine (1.1 mg/kg, i/v) anaesthesia was induced by rapid injection of ketamine at a dose of 2.2 mg/kg intravenously. Anaesthesia was maintained by halothane. Serially collected blood samples were analysed by gas liquid chromatographic technique. Plasma ketamine concentrations declined biexponentially with a rapid initial distribution phase ($t\frac{1}{2}$ = 2.89 ± 0.25 min.) followed by slower elimination phase ($t\frac{1}{2}$ = 68.84 ± 3.46 min.). Norketamine found in all horses, while there was very little dehydronorketamine detected.

Woldroth and Fudens (1972) used ketamine hydrochloride as an anaesthetic in laboratory rabbits, rats, mice and guinea pigs. In all species, intramuscular doses of 44 mg/kg ketamine provided adequate anaesthesia for surgical procedures requiring 15-25 min. operating time. Induction time was 8-10 min. and recovery was complete in 30-45 min. after injection. Intramuscular

injection of 22 mg/kg provided adequate anaesthesia for a variety of procedures.

Livingston and Waterman (1978) reported that the sleeping time was decreased in rats with 10 daily injections of ketamine (40 mg/kg). The decrease in sleeping time was associated with more rapid decrease in circulating and brain levels of ketamine and N-methylated product. This indicate that tolerance to ketamine in rats is associated with increased hepatic metabolism.

Porter (1982) observed the haematologic and rectal temperature values in Rhesus monkeys while immobilized with either ketamine (15 mg/kg) or ketamine-acepromazine (11 mg/kg and 0.55 mg/kg) respectively. Immobilization time were compared with test groups. Only neutrophil count was found to be statistically different. Acepromazine-ketamine combinations offered certain advantages over ketamine used alone.

Thurmon et al. (1972) reported that intramuscular injection of 13-20 mg/kg of ketamine in swine resulted in rapid immobilization.

Gallagher et al. (1985) conducted research on immobilization of collard peccaries with ketamine hydrochloride. 19 collard peccaries (Tayassu tajacu) were injected intramuscularly with ketamine hydrochloride (14.71 to 24.61 mg/kg) administered by cap-chur gun. First effect was observed in less than 5 min. Immobilization period was 71.7 min. Multiple doses were given to prolong immobilization period.

Denny (1973) reported that ketamine is a short acting anaesthetic in kangaroos. Dose of 15 mg/kg for the red kangaroos and 19 mg/kg for the euro, rapidly brought about surgical anaesthesia lasting for 20 min. The animal remaining immobilized for more than one hour.

Wilson and Warner (1976) reported that intramuscular ketamine is satisfactory for restraint and handling of pine marten and in high doses, for short duration of anaesthesia. At 7 mg/kg the righting reflex was lost for 9 min. during which time the animals were heavily sedated and could be easily handled.

Hunt (1976) used ketamine hydrochloride for anaesthetising European badger. Prolonged but light anaesthesia was induced in badger by subcutaneous injection of 26 mg/kg of ketamine. Sedation was induced in same animal with 14 mg/kg.

Kollias and McLoosh (1978) described the effects of ketamine HCl in red tailed hawks. Intramuscular dosage of 30 mg/kg ketamine did not significantly affect arterial blood gas and acid base values. It was a safe and effective immobilization agent at this dosage used.

Dosages of ketamine is inversely proportional to birds body weight (Doever and Wright, 1975). More than 90 birds with body weight ranging from 15 g to 45 g were used for the study. A concentration of 100 mg/ml was used. Restraint is considered as moderate CNS depression and the bird is calm.

Corneal and pedal reflexes were present. The birds were excited during recovery. Thrashing and lack of co-ordination, frenzied wing flapping and head shaking were noticed. Ketamine caused a decrease in body temperature, and is the best for procedures that required restraint or immobilization for short periods.

II.2. Xylazine

Clinical trial of xylazine was conducted in six horses and six cattle by Clarke and Hall (1969). A dose of 2 to 3 mg/kg appeared to be safe, reliable and short acting sedative for horses. Arterial carbondioxide increased in horses. In cattle, intramuscular injections of 0.05 to 0.1 mg/kg produced bradycardia and initial fall in cardiac output and no change in stroke volume. Xylazine caused a fall in respiration rate, breathing became laboured and deep.

Lane (1970) reported that the sedation of cattle with subcutaneous or intravenous injection of 10 adult bulls and cows with 1 to 8 ml of 2% xylazine solution produced sedation within 45 sec. to 25 min., which lasted for 2 to 6 h.

Dackal et al. (1975) studied the influence of xylazine on vital body functions in cattle. In six healthy adult cows rectal temperature, heart rate and respiration rates and reflexes were studied before and at 10, 20, 30, 60 min. and 24 h. after administration. ECG were taken in 5 min. intervals during anaesthesia. Blood constituents were also studied. Results indicated that xylazine caused no adverse effects.

Campbell et al. (1979) studied the haemodynamic effect of xylazine in calves. The effects included, immediate and prolonged reduction in heart rate, cardiac output, arterial blood pressure, total peripheral resistance, end diastolic left ventricular pressure, left ventricular residual function were increased. Sedative doses of xylazine in calves are smaller than in other species.

Mbiuki (1981) conducted studies to evaluate analgesic properties of xylazine. Nine bulls of about two years age weighing 200 to 300 kg were used. Each bull was given a 30 mg intramuscular injection of the drug before surgery to create a penile and preputial deviation. For 2 to $2\frac{1}{2}$ h. none of the bulls showed evidence of pain. Recovery was smooth and the animals started eating when they stood.

Physiologic and sedative effects of xylazine in buffaloes were studied by Pachin and Kumar (1979). Intramuscular administration of xylazine 0.22 mg/kg in buffaloes produced significant reduction in mean arterial pressure, heart rate and respiration rate. Pre-medication with atropine 0.04 mg/kg caused comparatively less reduction. Rectal temperature decreased slightly after its administration. Atropine premedication decreased the weak time, down time and complete recovery time. Xylazine caused mild depression of palpebral and swallowing reflexes, but severely depressed pinch reflex.

Tantawy et al. (1982) conducted some clinical studies on

xylazine (Rompun) in buffaloes. Intramuscular injection of xylazine at dosages of 0.02, 0.03, 0.05 or 0.07 mg/kg body weight were given. The most effective dosage was 0.03 mg/kg. Animal became docile for 15 min. and could be examined easily for 85 min. Body temperature increased after injection, while pulse rate, respiration rate and ruminal movements decreased.

Peshin and Kumar (1983) conducted researches on evaluation of haemocytological and biochemical effects of xylazine in buffaloes. Xylazine administered intramuscularly at 2.2 mg/kg. Blood cytology and biochemistry were studied before 30 min., 24 h and 72 h administration of xylazine. Slight decreases in total erythrocytes, leucocytes, packed cell volume and haemoglobin were observed.

Cardiopulmonary, haemocytological and biochemical effects of xylazine in goat were studied by Kumar and Thurmon (1979). Intramuscular administration of xylazine at 0.22 mg/kg body weight reduced the rate of breathing, without affecting the mean arterial pressure or rectal temperature. Pre-medication of atropine did not affect the depth and pattern of respiration but it decreased the heart rate. There was decrease in total erythrocytes, haematocrit and haemoglobin concentration, rise in neutrophils and decrease in lymphocytes. Blood changes returned to normal in 24-72 h.

Kerr et al. (1972) confirmed the use of xylazine as a good sedative in horses. Transient second degree A.V. block was induced at dosages of 0.55, 1.1 and 2.2 mg/kg. Atropine

sulphate (0.011 mg/kg) prevented the A.V. Block. Significant changes were not observed in respiration rate, arterial blood gas values. Cardiovascular effects like depressed heart rate, blood pressure and cardiac output were noticeable for at least 60 min. after intravenous injection.

Hoffman (1974) reported that xylazine administered intravenously to randomly selected 223 horses in a dose ranging from 0.25 to 0.75 mg/lb of body weight revealed that at 0.5 mg/lb (0.20 mg/kg) body weight intravenously xylazine produced consistent and predictable effects regardless of breed, age, sex and temperament. Maximum sedation occurred in 3 min. and lasted for 30 to 40 min. Sedation and analgesia were excellent in 81 per cent and good in 88 per cent.

McCashin and Gabel (1975) conducted experiment on evaluation of xylazine as a sedative preanaesthetic agent in horses. Xylazine administered intramuscularly at dose levels of 2 mg/kg was an effective sedative and pre-anaesthetic for thiamylal sodium narcosis and halothane anaesthesia. Cardiac and respiration rates were decreased and transient cardiac arrhythmias occurred. The onset of action was rapid, that is at 5 min. and maximum effect was resulted after 15 to 20 min.

Twenty-six unsedated horses were anaesthetised by intravenous administration of xylazine and ketamine (Muir et al., 1977). In all the horses heart rate, rhythm, respiration rate, deep rectal temperature, central venous pressure, pulmonary arterial pressure, cardiac output, arterial and venous pH and

partial pressure of blood gases were observed. Twenty-four animals were divided into three groups. Xylazine (1.1 mg/kg) followed by ketamine (2.2 mg/kg) after 3 to 5 min. was given intravenously to 19 horses. To the second group, xylazine (1.1 mg/kg) mixed with ketamine(2.2 mg/kg) was given. To the third group xylazine (1.1 mg/kg) followed by ketamine (6.6 mg/kg) was given. First and second group produced excellent analgesia and light anaesthesia in all horses. Larger doses of ketamine (6.6 mg/kg) were accompanied by muscle tremors, rigidity, mydriasis, sweating, hypertension, tachycardia and increased rectal temperature.

Kumar and Singh (1978) reported that xylazine is a sedative and analgesic agent in equine surgery. The effect of xylazine (2.5 mg/kg, i/m) was studied in 12 horses undergoing minor surgery under local procaine anaesthesia and in three normal controls. Sedation lasted for about 30 min. in controls and 45 min. in surgical cases. There was slight decrease in blood cell counts and haemoglobin concentration.

Locusta and Florae (1973) reported that after intravenous administration of xylazine (average 2.34 mg/lb body weight) in dogs, the period of induction was 30 to 90 sec. There was reduction in heart rate (50%) respiration rate (36%) and increase in body temperature (0.1 to 0.7°C) Drug produced hypnosis accompanied by analgesia and muscle relaxation.

Winstanly (1974) reported the use of xylazine as a central nervous system depressant in the dogs. From the clinical and

experimental trials it was found to be a good hypnotic, a mild sedative and could be used as a sedative in dogs.

Cardiopulmonary effects of xylazine in dogs was studied by Klide et al. (1975). Effects of xylazine were determined on arterial pH, arterial O_2 pressure, arterial carbondioxide pressure, stroke volume and peripheral resistance in dogs. After intravenous administration of xylazine 1.1 mg/kg, arterial pH, PaO_2, $PaCO_2$ values showed a change from the control. However, the drug did not produce a statistically significant decrease in heart rate and aortic flow, an increase in blood pressure followed by increase or decrease in peripheral resistance was observed.

Lecuita and Yan (1976) conducted a preliminary study on the pre-anaesthetic value of xylazine (Rompun) given intramuscularly in dogs prior to thiamylal sodium anaesthesia. Xylazine was given at a dose rate of 0.8 mg/kg i/m to 35 dogs. Sedation occurred after 6 to 11 min. Thiamylal sodium as a two per cent solution given to effect 10 min. after sedation. Satisfactory anaesthesia was attained in 29 min. In small dogs and puppies the dose of thiamylal sodium was reduced by as much as 75 per cent.

Xylazine injected intramuscularly at 3 mg/kg in rat, rabbit, and dogs decreased the number of erythrocytes, leucocytes, percentage of lymphocytes and increased percentages of neutrophils (Oh and Lee, 1984).

Omamegbe (1985) reported the use of xylazine for pre-medication in dogs. Xylazine (1 mg/kg i/m) followed after 10 min. by sodium pentobarbital (10 mg/kg i/v) produced excellent narcosis, muscle relaxation and analgesia to permit major surgery.

Lacuata and Leon (1973) conducted a preliminary study on the sedative effects of xylazine (Rompun) in cats. Xylazine produced sedation in cats when given at a dose rate of 1 mg/kg but caused vomiting. The induction time was 30 to 90 sec., vomiting time 1.5 to 1.8 min. and the sedative effect lasted for 40 to 60 min. after intravenous administration and 25 to 70 min. after intramuscular administration.

Colby et al. (1984) demonstrated the emetic action of xylazine on the chemoreceptor trigger zone for vomiting in cats. Xylazine induced vomiting was eliminated in cats by the ablation of the area postrema. It was concluded that xylazine acts on chemoreceptor trigger zone of the area postrema and this action may be mediated by opiate type receptors.

Immobilization of zoo animals was conducted by Bade (1974). He immobilized antelopes, gazelles and bovines with xylazine alone or followed by or combined with ketamine.

Haematological effect of xylazine in Bactrian camel was studied by Custor et al. (1977). Xylazine at a dose rate of 0.27 and 0.51 mg/kg body weight produced adequate sedation for various procedures. Haematological and serum biochemical values for camels restraint manually were compared with those

for camels restraint with xylazine. Xylazine treated camels had lower values for erythrocytes, haemoglobin and packed cell volume and higher blood glucose concentration.

Evaluation of xylazine for chemical restraint of captive artic wolves was conducted by Philo (1978). Xylazine at dosages of 2.7 to 3.9 mg/kg body weight was administered to 23 captive wolves (Canis lupus). The optimal dosage was comparatively high for excited and socialised adults. Mean time to initial effect was 25 min. and mean time to sternal recumbency was 37 min. Maximum effect was obtained within 15 min. Adequate sedation lasted for 30 to 60 min. Induction and recovery from anaesthesia was smooth and quiet.

Dongse (1979) sedated Asian elephants with xylazine. Doses of 100 to 300 mg of a 10 per cent solution of xylazine satisfactorily sedated six elephants ranging from 150 to 255 cm shoulder height. At this dosage all animals were sedated in the standing position. The initial signs of sedation ranged from 10 ± 4 to 20 ± 4 min. and the effect lasted from 60 ± 8 to 100 ± 15 min. Time taken from injection to complete recovery ranged from 360 ± 31 to 540 ± 21 min. Disturbances during induction delayed the onset of action of the drug.

II.3. Xylazine-ketamine

Amend et al. (1972) used xylazine pre-medication to eliminate muscular hypertonicity in cats during ketamine anaesthesia. Twenty adult cats were injected with xylazine followed by ketamine hydrochloride intramuscularly. Xylazine

eliminated muscular hypertonicity, prolonged the duration of analgesia at low doses of anaesthetic and provided sedation of sufficient duration to ensure quiet recovery.

A two per cent xylazine solution intramuscularly (0.5 mg/kg) in cats produced slight sedation. Ketamine (20 mg/kg) intramuscularly given 20 min. later produced general anaesthesia lasting for 25 to 50 min. (Karl,et al., 1974). There were decrease in body temperature, pulse rate, respiration rate and volume, erythrocyte counts and leucocyte counts. The ECG changes reported are attributed to hypothermia, hypoxia and parasympathomimetic effect of xylazine.

Cardiopulmonary function was assessed in healthy cats given xylazine-ketamine combination (Allen et al., 1986). Cardiac output, heart rate, stroke volume and cardiac index were significantly decreased.

Navarro and Freedman (1975) conducted clinical evaluation of xylazine and ketamine hydrochloride for caesarean in dogs. Xylazine did not quieten the puppies when used at a dosage of 0.5 to 1 mg/lb (0.2 to 0.4 mg/kg), but it provided sufficient analgesia and muscle relaxation to allow delivery of the litter. The pups so delivered were not sedated. Ketamine hydrochloride complemented the effect of xylazine and facilitated completion of surgery. However, the combination produced satisfactory sedation.

Anaesthesia of dog and cat with a combination of ketamine and xylazine at a dose rate of 15 mg/kg and 3 mg/kg

intramuscularly showed that the anaesthesia was of short duration (30 to 40 min.) but could be prolonged for three hours by intravenous administration (Haufman, 1976). Respiration slowed, corneal reflexes were absent. There were no vomiting or convulsions.

Lele and Bhokr (1983) conducted experiment on evaluation of xylazine as an anaesthetic agent in combination with pre-anaesthetic drugs in dogs. 3 mg/kg body weight of xylazine combined with triflupromazine (2.2 mg), chlorpromazine hydrochloride (1 mg) and diazepam (2 mg) respectively to each group. Each drug is administered prior to xylazine administration. Respiration rate decreased in all groups. Blood pressure lowered with administration of pre-anaesthetics but improved slightly by xylazine. Heart rate increased initially with pre-anaesthetic drugs, but significantly dropped after xylazine administration. Xylazine caused slight increase in rectal temperature.

Clinical studies of ketamine hydrochloride and xylazine hydrochloride in domestic goats showed that the combination induced anaesthesia for a variety of surgical procedures including laparotomy, enucleation of eye ball, amputation of claws, abomasotomy and enterotomy (Kumar et al., 1976). Dose of xylazine and ketamine used was 0.22 mg/kg body weight and 11 mg/kg body weight, respectively, although respiration rate, heart rate and rectal temperature were decreased. They remained within normal limits. Surgical anaesthesia was

maintained for 2.25 to 2.75 h. by supplemental increments of ketamine or a mixture of xylazine and ketamine. Skeletal muscle relaxation was good in all animals and recovery was smooth and uncomplicated.

Bygagaire and Mbiuki (1984) reported that the duration of analgesia in sheep is longest by intramuscular administration of ketamine and xylazine. Dosage of ketamine and xylazine used were 11 mg/kg and 0.22 mg/kg respectively. The same dosage was given by intramuscular and intravenous route. Longest duration by intramuscular injections and least average analgesic time by intravenous administration.

White and Holmes (1976) conducted comparative study of ketamine and ketamine-xylazine for effective surgical anaesthesia in rabbit. A dose of 44 mg/kg ketamine in 10 rabbits did not produce sufficient muscle relaxation for ventral abdominal incisions. Adequate anaesthesia for these operations were obtained with a combination of 35 mg/kg ketamine plus 5 mg/kg xylazine which produced a sleep like state lasting upto four hours and surgical anaesthesia for 20 to 75 min.

The combination of ketamine and xylazine was tested in adult mice (Mulder and Mulder, 1979). The combination of xylazine and ketamine was prepared by mixing 1 ml of ketamine (100 mg/ml), 1 ml of xylazine (100 mg/ml) and 46 ml of sterile water. For 30 g body weight 0.1 ml of the combination was used to provide 50 mg/kg of each drug. Noted the time of induction, duration and recovery. Mean induction time was 5 min. Mean

anaesthesia for 8 min. Adequate anaesthetic level can be maintained for 60 to 100 min.

Beverly and Vargo (1980) reported the use of ketamine-diazepam and ketamine-xylazine combination in Guinea-pig. The two combinations were used in the following dosages. 44 mg/kg body weight of ketamine with 0.1 mg/kg diazepam and 25 mg/kg ketamine with 5 mg/kg xylazine. The drugs were mixed and injected intramuscularly. Both combinations abolished signs of pain from all animals. Recovery time was prolonged with ketamine-xylazine than with ketamine-diazepam combinations.

Twenty-six adult horses were used to investigate intravenous anaesthesia by xylazine and ketamine (Muir et al., 1977). Xylazine 1.1 mg/kg followed by rapidly 2.2 mg/kg ketamine provided quick, safe and excellent analgesia and short duration of anaesthesia. Recovery was uneventful. Larger doses of ketamine were unsatisfactory. Larger doses of ketamine (6.6 mg/kg) following sedation with xylazine (1.1 mg/kg) intravenously, were accompanied by muscular tremors, rigidity, mydriasis, oculogyric movements, sweating, hypertension, tachycardia and increased rectal temperature during recovery.

Pre-medication with xylazine five minutes before or concurrently with ketamine in horses give similar results but if intraval is more than five minutes between the drugs produced less deep anaesthesia (Fisher, 1984).

Kumar and Singh (1979) reported that ketamine at 11 mg/kg intramuscularly preceded by xylazine 0.22 mg/kg intramuscularly

in calves produced good surgical anaesthesia lasting for 40 to 85 min. There were slight reduction in respiration rate, heart rate, and temperature during anaesthesia.

In calves ketamine injected intravenously at 11 mg/kg had very little effect on heart rate, respiration rate, arterial blood pressure, central venous pressure, blood gases and body temperature (Acuad et al., 1981). Xylazine at 0.23 mg/kg intramuscularly caused a brief initial rise in blood pressure followed by decrease in respiration rate, blood pressure and oxygen tension. A combination of ketamine 2.85 mg/kg and xylazine 0.14 mg/kg resulted in initial rise in heart rate, respiration rate and blood pressure. This low dose combination was effective in inducing surgical anaesthesia.

General anaesthesia produced by a combination of xylazine and ketamine was evaluated in 24 cattle (Mbiuki, 1982). The drugs were given intramuscularly or intravenously either at 10 min. interval or mixed together. Xylazine dosage was 0.1 mg/kg by both routes and ketamine was given at 6 mg/kg intramuscularly and 2 mg/kg intravenously. Mean recovery time ranged from 30.8 min. to 63 min. Duration of analgesia ranged from a mean of 8.3 min. at the coronet to a mean of 66 min. at the paralumbar fossa. Muscular relaxation was poor. Heart rate normal, rectal temperature and respiration rate varied.

The dosages of xylazine and ketamine as a knock down agent in lion were 3 mg/kg body weight for ketamine plus 2.5 mg/kg body weight for xylazine (Kock, 1984).

Treatment of wound on the forelimb of a lion (Panthera leo) under general anaesthesia was done by George et al. (1986). After securing the animal within the cage, xylazine hydrochloride 10 per cent solution 10 ml (i.e. at a dose of 10 mg/kg body weight) followed by atropine sulphate 40 mg were injected intramuscularly. The animal assumed unsteady gait by the fifth min., sternal recumbency in another two min. and lateral recumbency by the 11th min.

When ketamine-xylazine combination was administered, emesis was observed in two out of three lions (Panthera leo) during induction and in all animals during recovery (Cheeran et al., 1989).

Ketamine injected intramuscularly into deer mouse (Peromyscus maniculatus) at 100 mg/kg produced adequate general anaesthesia but inadequate analgesia. This deficiency was rectified by combining ketamine and xylazine both at 50 mg/kg (Silverman and Ingram, 1986).

White et al. (1987) studied the effect of i/m administration of xylazine (0.25 mg/kg), ketamine (5.5 mg/kg) and a mixture of xylazine 0.15 mg/kg and ketamine (2.5 mg/kg) on sedation, analgesia, cardiac and respiration rates, body temperature and muscle relaxation in dromedary camel. The mixture of ketamine and xylazine was superior to either drug used alone.

The surgical management of an wound on the tongue of a captive bonnet monkey under general anaesthesia using a

combination of xylazine (2 mg/kg) and ketamine (6.25 mg/kg) was done by George et al. (1987). Both the drugs were administered intramuscularly. The animal was unsteady within three minutes and assumed lateral recumbency by fourth minute.

Cheeran et al. (1989) reported that out of 121 captive musth elephants tranquillized and translocated, 94 elephants were immobilized with xylazine (100 mg/ton), 17 elephants with acepromazine and xylazine (50-60 mg/ton and 100 mg/ton), two elephants with xylazine and diazepam (100 mg/ton and 7 to 20 mg/ton) and eight elephants with xylazine and ketamine (100 mg/ton each).

II.4. Ketamine-xylazine-yohimbine

Xylazine sedation can be antagonized by 4-aminopyridine and yohimbine (Hatch et al., 1982). Groups of fasted atropinised dogs of both sexes were given a standard dosage (2.2 mg/kg body weight) of xylazine intramuscularly. After full sedation the dogs were given intravenous 4-aminopyridine (0.3 mg/kg), yohimbine (0.125 mg/kg) or a combination of both. Control group was given saline solution. 4-aminopyridine decreased the mean walk time to 6 min. (saline treated groups 14.1 to 17.8 min.) and total recovery time to 2.5 h. Yohimbine decreased the walk time to 2.2 min. and total recovery time to 0.4 h (saline treated groups 0.8-2.7 h).

Complete immobilization produced in dogs by xylazine-atropine could be reversed by 4-aminopyridine and yohimbine

(Wallner et al., 1982). Cross-bred dogs of both sexes were given intravenous injection of a standard dose of xylazine (2.2 mg/kg). When fully sedated the dogs were given intravenous injection of a large dose of (0.5 mg/kg) atropine sulphate. When fully immobilized the dogs were injected intravenously with saline (control), 4-aminopyridine (0.03 mg/kg), yohimbine (0.125 mg/kg) or a combination of both. Mean walk time were 76 min. for the control, 25.4 min. for 4-aminopyridine administered group, 8.7 min. for those given yohimbine and 4.8 min. for those given 4-aminopyridine and yohimbine. Mean total recovery time was 3.8, 2.5, 1.1 and 1.6 h. respectively.

Cronin et al. (1983) reported that acepromazine-xylazine sedation in dogs can be antagonized with 4-aminopyridine and yohimbine. Standard dose range of xylazine-acepromazine combination was 2.2 mg/kg, 0.5 mg/kg respectively. Loss of righting reflex was considered to be a point of maximum sedation. These dogs were injected intravenously with 4-aminopyridine (0.5 mg/kg), yohimbine (0.25 mg/kg) or a combination of 4-aminopyridine and yohimbine. Control group was given intravenously one ml saline solution. The 4-aminopyridine, yohimbine and 4-aminopyridine with yohimbine reduced the walk time from control value of 43.1 min. to 7.6, 4.4 and 1.9 min. respectively. Increased heart rate was also observed in intact dogs given yohimbine. There were increase in rate and depth of respiration.

Yohimbine, an adrenoceptor blocking agent given intravenously (0.1 mg/kg) in dogs antagonized bradycardia, but potentiated xylazine induced hypotension (Hsu et al., 1985). Xylazine caused decrease in heart rate, accompanied by sinus arrhythmia and initial increase in arterial blood pressure which was followed by decrease.

Hatch and Ruch (1974) found that in cats anaesthetised with ketamine (20 mg/kg) intravenously, the duration of anaesthesia was reduced by amphetamine and yohimbine. Ambulation time was not shortened by these drugs. A mixture of amphetamine and yohimbine, antagonized ketamine almost immediately. Ketamine induced cataleptic motor impairment was not antagonized by the mixture.

Twelve cats were used to evaluate the effect of yohirbine an antagonist of xylazine (Hsu and Lu, 1984). Two intramuscular dosages of xylazine and ketamine (2.2 mg/kg of xylazine plus 6.6 mg/kg ketamine and 4.4 mg/kg of xylazine plus 6.6 mg/kg ketamine) caused approximately 60 and 100 min. of anaesthesia respectively. When yohimbine was given 45 min. after ketamine administration, cats regained consciousness within three minutes. They were walking within 1 to 2 min. after regaining consciousness. Yohimbine reversed the bradycardia and respiratory depression caused by xylazine. Yohimbine is also useful for controlling the duration of xylazine-ketamine anaesthesia in cats.

Kitzman et al. (1982) reported that xylazine sedation can

be antagonized by 4-aminopyridine and yohimbine in cattle. Twenty-four cross-bred steers were injected intramuscularly with standard dosage range of xylazine hydrochloride (0.2 to 0.3 mg/kg body weight). These animals were grouped into four. When sedated maximally, the first group was given isotonic saline solution (1 ml, i/v), group II was given 4-aminopyridine (0.3 mg/kg, i/v), group III was given yohimbine (0.125 mg/kg i/v) and group IV was given 4-aminopyridine plus yohimbine in the same dose as above. The 4-aminopyridine decreased the mean standing time from 94.3 min. to 73.4 min. Yohimbine decreased the mean standing time to 27 min. Mean total recovery time were not significantly decreased.

Xylazine (0.15 mg/kg) resulted in significant respiratory depression and decrease in arterial partial pressure in sheep. Yohimbine (0.125 mg/kg) produced a significant improvement in partial pressure of oxygen in 50 min. and abolished the paradoxical respiratory pattern (Doherty et al., 1986).

The ability was compared of tolazoline and yohimbine to antagonize xylazine induced central nervous system depression, bradycardia and tachypnoea, in nine ewes and five rams. Each sheep received 0.4 mg/kg xylazine followed in 10 min. by 2 mg/kg tolazoline or by 0.2 mg/kg yohimbine. Xylazine alone caused recumbency for 41 $\pm$ 3.7 min. Tolazoline and yohimbine shortened the xylazine induced recumbency to 12.1 $\pm$ 0.9 and 18.1 $\pm$ 1.5 min. respectively. Both tolazoline and yohimbine reversed bradycardia and tachypnoea (Hsu et al., 1987).

Antagonism of xylazine and ketamine anaesthesia by 4-aminopyridine in gelding was reported by Kitzman et al. (1984). Thirty-six geldings when maximally sedated were given saline solution, 4-aminopyridine (0.2 mg/kg), small dose yohimbine (0.075 mg/kg), large dose yohimbine (0.15 mg/kg) and 4-aminopyridine plus low dose yohimbine. Groups given 4-aminopyridine alone and small dose or large dose yohimbine alone produced a significant decrease in mean standing time (9.9 ± 1.6 min., 11.3 ± 7 min. and 10.6 ± 2.3 min. respectively) compared with that of saline control group (24.3 ± 9.2 min.). Mean total recovery time was not significantly different. 4-aminopyridine plus small dose yohimbine and large dose yohimbine produced significant decrease in mean standing time compared with that of the control (10.3 ± 2 min. and 8.3 ± 2.6 min. respectively). The mean total recovery time was significantly larger in the combine antagonist group compared with that of the control.

Schmidt (1983) reported a case of effective reversal of xylazine sedation with yohimbine and 4-aminopyridine in an adult female elephant. A total dose of 1200 mg of xylazine intramuscularly plus 600 mg intravenously (0.33 mg/kg) resulted in heavy sedation. After 50 min. of sedation 425 mg of yohimbine and 1000 mg of 4-aminopyridine were administered intravenously. The elephant was up and walking within 5 min. of antagonist administration.

Jacobson (1985) studied the effects of yohimbine on

combined xylazine-ketamine induced sedation and immobilization in juvenile African elephants. Twenty-two juvenile African elephants were given a combination of xylazine (0.14 ± 0.03 mg/kg of body weight) and ketamine (1.14 ± 0.21 mg/kg) as a single intramuscular injection. Immobilized animal had a mean immobilization time of 11.6 ± 6.9 min. 12 of the 14 elephants immobilized with a single dose combination of xylazine and ketamine were given yohimbine (0.13 ± 0.03 mg/kg) intravenously and remaining two elephants were allowed to recover spontaneously. The elephants given yohimbine had a mean standing time of 2.4 ± 1.1 min.

Renecker et al. (1985) immobilized four captive moose (Alces alces), four mule deer (Odocoileus hemoeinus) and five white tailed deer (Odocoileus virginianus) with xylazine (0.63 to 1.29 mg/kg body weight, i/m). Mean induction time for moose was 17 min. and for the deer, 14 and 10 min. respectively. In this study, maximal sedation of the moose and deer was reversed with successive injections (given i/v) of yohimbine (0.15 mg/kg) and 4-aminopyridine (0.26 to 0.29 mg/kg). These produced sternal recumbency to arousal intervals of 1 to 15 min. and recumbency to standing or walking intervals of 1 to 24 min. The injections of the reversal drugs produced marked increase in respiration rate and heart rate in the moose and deer, without occurrence of muscle tremors or convulsions.

Jessup et al. (1983) reported that ketamine at a dosage of 5.8 to 14.5 mg/kg and xylazine 0.44 to 0.92 mg/kg were

sufficient for effective immobilization in mule deer. Recumbency achieved in 95 min. Ambulatory time was 150 min. Yohimbine at a dose rate of 0.125 mg/kg produced effective reversal. Mule deer became ambulatory in 1 to 17 min. (average 8.2 min.).

Effect of yohimbine on xylazine induced immobilization in white tailed deer was studied by Hsu and Sheerlaw (1984). 24 white tailed deer were given intramuscular injections of xylazine (2.8 ± 1 mg/kg). Yohimbine at various times were given to evaluate its effects on xylazine induced immobilization. In five control deer were given 3.7 ± 1.2 mg of xylazine per kg. Onset of recumbency was 13 ± 2 min. and the time of standing was 268 ± 76 min. Time for sitting after yohimbine was 3 ± 7 min. and the time for standing was 4 ± 5 min. Yohimbine also reversed the bradycardia and respiratory depression induced by xylazine.

Moch et al. (1985) reported that white tailed deer (Odocoileus virginianus) immobilized with ketamine hydrochloride (3.70 ± 1.4 mg/kg and 0.54 ± 1.99 mg/kg respectively) can be effectively reversed by the administration of 0.09 to 0.53 mg/kg of yohimbine hydrochloride intravenously. The deer raised their heads with an average time of 2 min. The animals stood in 6 min. and walked away in 9.5 min.

Ramsay et al. (1985) used yohimbine hydrochloride to reverse immobilization of polar bears by ketamine hydrochloride and xylazine hydrochloride. Single intravenous dose of yohimbine hydrochloride ranging between 0.029 and 0.198 mg/kg

resulted in a median time of 10 min. to post-injection recovery from ketamine hydrochloride and xylazine hydrochloride immobilization. Convulsions and muscle twitching occurred in some animals. Median respiration rate and heart rate increased from 5 to 12 breaths per min. and 51 to 79 per min. respectively.

Reversal effect of xylazine by administration of alkaloid yohimbine either alone or in combination with 4-aminopyridine in red deer has been studied by Mckelvey and Simpson (1985). Intravenous administration of yohimbine (0.15 to 0.2 mg/kg) and 4-aminopyridine (0.3 to 0.5 mg/kg). The time elapsing after injection of reversal agent to adopt sternal recumbency and the time for standing were noted. The natural recovery mean time for standing were 242 $\pm$ 39.3 min. After injection of antidote the recovery time were 14.9 $\pm$ 3.5 min.

Failure of yohimbine to reverse ketamine has been reported by Lynch and Line (1985). Nine adult female rhesus monkeys were given an intravenous dose of either 0.5 mg/kg yohimbine hydrochloride or saline 10 min. after intramuscular administration of 10 mg/kg ketamine hydrochloride. There was no difference in the duration of anaesthesia.

Kreeger and Seal (1986) reported that yohimbine failed to reverse immobilization in grey wolves. Yohimbine (0.2 mg/kg) was given intravenously 15 min. after immobilization with ketamine (25 mg/kg). Although the animals given yohimbine raised their head significantly earlier than controls, there was no differences in time taken to walk.

Hsu et al. (1986) administered xylazine (21 mg/kg) and ketamine (45 mg/kg) intramuscularly to 12 Sprague-Dawly rats. Anaesthesia lasted approximately for 70 min. There was polyurea, bradycardia and bradypnoea. Yohimbine (2.1 mg/kg) was administered intramuscularly 20 min. after xylazine-ketamine injection. Rats regained consciousness and righting reflexes within 10 min.

Six tigers (Panthera tigris tigris) were immobilized five times at two week interval with ketamine at different dose levels. There were acute changes in hematocrit, chloride, potassium, glucose and bilirubin in blood. Yohimbine produced recovery within 4.8 min. Yohimbine at 5 to 15 mg/kg in adult tiger gave effective reversal of 50 to 150 mg of xylazine (Seal et al., 1987).

II.5. Buprenorphine

Taylor and Houlton (1984) conducted a study on post-operative analgesia in dogs. Dogs of many breeds were given pentazocine (1 mg/kg), buprenorphine (6 µg/kg) and morphine (0.2 mg/kg) to control the post-operative pain after ortho-podic surgery. There were significant decreases in respiration rate at 30 min. and 2 h. after buprenorphine and 4 h after morphine and pentazocine.

In some animal tests, buprenorphine decreased the respiration rate and increased arterial $PaCO_2$ with decreasing arterial PaO_2 (Cowan et al., 1977a).

Buprenorphine showed a bell shaped dose response curve. Increasing dosages produced increased responses and after attaining a maximum response, still larger doses produced lesser activity than smaller doses (Heel et al., 1980).

Cowan et al. (1977) found that buprenorphine reduced the heart rate, but had no effect on arterial blood pressure in conscious rats and dogs. In cats buprenorphine (0.10 and 1.0 mg/kg) caused no major haemodynamic changes. With doses of buprenorphine greater than 0.10 mg/kg the duration of respiratory depression becomes less. Ceiling effect occurred such that the maximum effects produced were less than those obtained with morphine.

Nolan and Hall (1984) studied the effect of four intravenous combinations, xylazine (0.7 mg/kg) and methadone (0.1 mg/kg), xylazine (0.7 mg/kg) and buprenorphine (0.004 and 0.006 mg/kg and acepromazine on arterial blood pressure, central venous pressure, heart rate, respiration rate and blood gases were studied in four ponies. With xylazine-buprenorphine and xylazine-methadone the onset of sedation was rapid. Onset of sedation after intravenous injection of acepromazine buprenorphine was slower.

Piercy (1985) reported that buprenorphine is an effective analgesic in both cat and dog. It is useful especially before orthopedic surgery or anal gland removal and have been found that it gives smoother post-operative period. It is used along with acetylpromazine intramuscularly to sedate dogs.

Stock (1985) reported the use of buprenorphine hydrochloride in combination with acetylpromazine in dogs and cats, as a premedicament. It does not cause respiratory depression and untoward cardiovascular effects. Although the analgesic properties are said to last six to eight hours, the sedative effect last over 18 hours.

Taylor (1985) reported that buprenorphine has some sedative effect and no excitement. Vomiting may occur in man. Some respiratory depression is seen; but less severe than morphine.

Taylor and Herrtage (1986) conducted evaluation of some drug combinations for sedation in the dogs. Drug combinations used were acepromazine-pethidine (70 µg/kg and 3.3 mg/kg) acepromazine-buprenorphine (70 µg/kg and 9 µg/kg) and acepromazine (130 µg/kg) alone. The degree of sedation, resistance to manipulation, sensitivity to noise and response to pain were assessed. The combination of acepromazine with buprenorphine or pethidine produced better sedation.

II.6. Pentazocine

Davis and Sturm (1970) observed that the peak concentration of pentazocine were similar in all species except in cats in which peak concentration was higher. Sialosis, mydriasis, emesis, polypnoea and central nervous depression were the effects observed. In dogs profuse salivation and diarrhoea were observed. Peak plasma concentration at 15 min. in goats, dogs and swine and 60 min. in cat.

Benitez and Brunel (1973) observed the effects of pentazocine in dog and cat. The analgesic properties were tested in 20 dogs, which were given 0.5, 1 and 2 mg/kg body weight intravenously and in 10 cats which were given 3 mg and 4 mg/kg subcutaneously. The results were measured as a mean time threshold for response to the application of a heated copper plate to the median aspect of the thigh.

Cooper and Organ (1977) used six beagles to compare the effects of pentazocine 15 mg and 30 mg for each dog. Both doses produced no adverse effects, but 30 mg dose produced adverse side effect after 8 h. and complete recovery in 12 h in both cases. Pentazocine at 4 mg per kg four times a day produced sedation, ataxia, slight salivation and increased respiration. But 6 mg/kg produced prostration and tremors.

Miner and Losacco (1984) proved that pentazocine lactate is safe and effective analgesic in dogs suffering from pain. Intramuscular administration at dosages ranging from 0.75 to 1.5 mg/kg rapidly produced analgesia for three hours. Adverse reaction noticed was salivation.

Muir and Robertson (1985) observed the visceral analgesic, cardiorespiratory and behavioural effects induced by xylazine (1.1 mg/kg), butorphanol (0.2 mg/kg), meperidine (1 mg/kg) and pentazocine (0.99 mg/kg) intravenously in adult horses with colic. Heart rate, respiration rate and mean arterial pressure were increased. The duration of visceral analgesia was long with xylazine (90 min.) followed by butorphanol (60 min.) and then meperidine and pentazocine (30 to 35 min.).

CHAPTER III

Materials and Methods

MATERIALS AND METHODS

The experiments were carried out in three different parts.

III.1. Determination of the ED_{50} xylazine, buprenorphine and pentazocine in rats and mice

In the first part, the ED_{50} of the three drugs namely, xylazine[1], buprenorphine[2] and pentazocine[3] were determined using the thermal stimulus method of Dandiya and Menon (1963) in rats and the tail clip method of Bianchi and Franceschini (1954) in mice.

III.1.A. Thermal stimulus method in rats.

The method described by Dandiya and Menon (1963) was followed. The analgesiometer[4] was used to assess the analgesic effect in rats (tail flick method). This has Nichrome wire which could be heated to the required temperature and maintained by means of heat regulator. The current passing through the Nichrome wire is indicated on the ammeter which indirectly gives the temperature of the wire. A jacket surrounds the

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1. Rompun - Xylazine hydrochloride - 500 mg dry substance - Bayer Leverkusen, Germany.
2. Tidigesic - Buprenorphine hydrochloride - 1 ml ampoule containing 0.3 mg - Tamil Nadu Dadha Pharmaceuticals Ltd., Tamil Nadu.
3. Fortwin - Pentazocine lactate - 1 ml ampoule containing 30 mg - Ranbaxy Laboratories Ltd., Dewas, M.P.
4. Analgesiometer - Techno Analgesiometer, Type MK-1, Techno Electricals, Lalbagh, Lucknow-1.

Nichrome wire and water is circulated through it. The upper surface of the jacket serves as a platform on which the tail of the rat can be placed. The water circulating through the jacket prevents the platform from getting heated up. This ensures that only that portion of the tail which lies just above the hot wire is affected.

The ammeter was set to four amperes so that the heat produced in the Nichrome wire was constant throughout the experiment. The rat was kept in a rat holder with only the tail portion protruding out. The tail was placed on the platform so that the middle portion of the tail remained just above the hot wire, but without touching it. The reaction time was noted when the animal responded with a sudden and characteristic flick or tail lifting.

Ten rats in a group were taken for each trial. The rats were weighed and the dose for each drug was calculated. A number of trials were conducted to determine the maximum dose that evoked no response in all the animals and the minimum dose that evoked positive response in all animals in the group.

The reaction time, that is the time taken for characteristic tail lift was measured to the nearest of the second before intraperitoneal injection of the drug, at 10 and 30 minute for xylazine, 10, 30 min., 1 h, 3 h and 6 h for buprenorphine and 10, 30 min., 1 h, 2 h, 3 h for pentazocine. Normal reaction time was noted for all the rats before administration of the drug. All the rats which were not responding within 10 sec.

were discarded. The response was considered as positive when the reaction time exceed the normal reaction time within 10 min. and 30 min. after intraperitoneal administration of the drug.

The experiment was first conducted on a trial group by injecting normal saline solution at a rate of 0.2 ml per rat to serve as a control in each set of experiments with different drugs. All the rats showed negative response.

In order to assess the approximate effective dose of each drug, six group of 3 rats each were taken for each drug and graded doses of each drug were injected into each group and the effects were noted.

After fixing the range of effective dose by the above trials, the experiment to study the ED_{50} was carried out, using a batch of 10 rats each.

III.1.B. Tail clip method in mice.

The method described by Bianchi and Franceschni (1954) was followed in this experiment using mice. A small bull dog clamp was applied at the base of the tail. The clip should exert the optimum pressure on the tail, i.e. which caused all the control mice to respond by attempting to dislodge the clip. The same clip was used throughout the experiment.

Five minutes after administration of the drug the clip was applied for 30 sec. Untreated animals made continuous efforts to dislodge the clip by biting. Analgesics cause the mice to be indifferent to the clip.

Unresponsive mice were screened out by testing all mice with the tail clip, those that did not commence continuous efforts to remove the clip within 15 sec. were discarded. Responsive mice were tested again just before administration of the drug. If no attempt to remove the clip was made at 30th min. after administration of the drug, the response was considered as positive.

The drugs were injected intraperitoneally according to body weights. The strength of the drugs were so adjusted as to give not more than a volume of 0.2 ml per mice weighing average 20 g.

A group of 10 mice were injected with 0.2 ml of normal saline per 20 g body weight to serve as control in each set of experiments with different drugs and the animals tested showed a negative response.

In order to fix the approximate effective dose range, different groups of two mice each were taken and each drug was administered in varying doses.

After fixing the range of effective dose by the above trials, the experiments to study ED_{50} were carried out on the following lines.

III.1.A.a. ED_{50} of buprenorphine in rats.

Rats divided into six groups of 10 each were used. Each group were given 0.03375, 0.0625, 0.125, 0.25, 0.5 and 0.75 mg/kg body weight of buprenorphine intraperitoneally and the results were recorded.

III.1.A.b. ED_{50} of pentazocine in rats.

Rats divided into six groups of 10 each were used in this experiment and were given 15, 20, 25, 30, 35 and 40 mg/kg body weight of pentazocine intraperitoneally and the results were recorded.

III.1.A.c. ED_{50} of xylazine in rats.

Fifty rats were divided into five groups containing 10 each and xylazine was administered intraperitoneally at dose rates of 0.25, 0.5, 1, 2 and 3 mg/kg body weight to each group respectively and the results were recorded.

III.1.B.a. ED_{50} of buprenorphine in mice.

Mice divided into five groups of 10 each were used in this experiment. Each group was given 0.25, 0.5, 0.75, 1 and 1.5 mg/kg body weight of buprenorphine and the results were recorded.

III.1.B.b. ED_{50} of pentazocine in mice.

Sixty mice were divided into six groups containing 10 each and each group was given 20, 30, 40, 45, 50 and 60 mg/kg of pentazocine respectively intraperitoneally and the results were recorded.

III.1.B.c. ED_{50} of xylazine in mice.

Sixty mice were divided into six groups each containing 10 mice. Xylazine was administered at a dose of 2, 4, 6, 8, 10 and 12 mg/kg body weight to each group intraperitoneally and the results were recorded.

III.1.c. Statistical analysis.

The data were analysed using Probit analysis (Finney, 1981).

III.2. Study of the influence of buprenorphine, pentazocine and xylazine on ketamine anaesthesia in dogs

III.2.A. Experimental animals.

Twenty-four apparently healthy pariah dogs of either sex weighing 8-20 kg were used for the study. All the animals were housed separately in cages, under identical conditions of feeding and management.

These 24 animals were divided into four groups of six animals each and were numbered.

Group A : A(1), A(2), A(3), A(4), A(5) and A(6)

Group B : B(1), B(2), B(3), B(4), B(5) and B(6)

Group C : C(1), C(2), C(3), C(4), C(5) and C(6)

Group D : D(1), D(2), D(3), D(4), D(5) and D(6)

The animals were weighed before the experiment and the dose was calculated according to the body weight. Ketamine[5] was administered alone intramuscularly (Group A) along with xylazine (Group B) along with buprenorphine (Group C) and along with pentazocine (Group D).

III.2.B. Preparation of the animals.

When the animal was quiet, basal measurements of temperature, pulse and respiration were taken and venous blood

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5. Ketalar - Ketamine hydrochloride - 50 mg/ml - Parke Davis Ltd., Bombay.

was taken from the saphenous or cephalic vein to study haematological parameters.

After recording the basal values, the drugs were administered intramuscularly into the thigh muscle as detailed hereunder:

Group A : Ketamine hydrochloride was administered at a rate of 20 mg/kg body weight (K)

Group B : Ketamine hydrochloride 15 mg/kg was administered to animals pretreated with xylazine hydrochloride 2 mg/kg, 5 minutes before ketamine (X-K)

Group C : Ketamine hydrochloride 15 mg/kg was administered to animals pretreated with buprenorphine hydrochloride 0.03 mg/kg 30 minutes prior to ketamine (B-K).

Group D : Ketamine hydrochloride 15 mg/kg was administered to animals pretreated with pentazocine lactate 2 mg/kg 15 minutes prior to ketamine (P-K).

III.2.C. The main items of observation

III.2.C.a. Time of sternal recumbency

III.2.C.b. Clinical signs namely,

Disappearance of reflexes

Temperature

Pulse

Respiration

III.2.C.c. Duration of anaesthesia

III.2.C.d. Regaining of sternal recumbency

III.2.C.e. Mean standing time

III.2.C.f. Total recovery time

III.2.C.g. Haemogram

Total erythrocyte count

Total and differential leucocyte count

Haemoglobin content

Packed cell volume

Observations were recorded before the administration of drug and after at intervals of 5, 10, 15, 30, 45, 90, 120 min. and blood samples were collected before the experiment as well as 30 min. and 24 h after the administration of the drug.

Methods

The volume of all the drugs administered are calculated based on the body weight and administered intramuscularly at the gluteal muscle of dog.

III.2.C.a. Time of induction.

It was calculated from the time of administration of the drugs to the time of disappearance of rectal reflexes in the case of xylazine and time of attainment of sternal recumbent posture in the case of ketamine.

III.2.C.b. Clinical signs

Disappearance of corneal, palpebral and pedal reflexes, sternal recumbency were the criteria for deciding the onset of anaesthesia.

The rectal temperature was recorded using the clinical

thermometer, pulse rate is recorded by palpating the femoral artery and the respiration by noting the chest movements.

III.2.C.c. Time of regaining of sternal recumbency

It was calculated from the time of administration of the drug to the time of the regaining of sternal recumbent posture during recovery.

III.2.C.d. Duration of anaesthesia

It was calculated from the time of sternal recumbency to the time of regaining of sternal recumbency.

III.2.C.e. Mean standing time

It was calculated from the time drug administration to the standing time.

III.2.C.f. Time for complete recovery

It was calculated from the time of administration of the drug to the time at which the animal is steady on its all four limbs.

III.2.C.g. Haemogram

Total erythrocyte count, total and differential leucocyte count and haemoglobin were estimated as per the technique described by Schalm (1975). Packed cell volume was estimated following the method of Wintrobe (1961).

III.2.D. Statistical analysis.

The data were analysed using CRD for assessing the differences within the group and for comparing the groups. Students 't' test were used.

III.3. Reversal of anaesthesia using yohimbine

Third part of the study consisted of reversal of anaesthesia using the $\alpha 2$ blocker yohimbine.

III.3.A. Experimental animals.

For this 24 animals either sex weighing (8-23 kg) were divided into four groups each consisting of six animals.

Group E : E(1), E(2), E(3), E(4), E(5) and E (6)

Group F : F(1), F(2), F(3), F(4), F(5) and F(6)

Group G : G(1), G(2), G(3), G(4), G(5) and G(6)

Group H : H(1), H(2), H(3), H(4), H(5) and H(6)

III.3.B. Preparation of the animal.

As in the second part of the experiment, ketamine, ketamine-xylazine, ketamine-bupronorphine and ketamine-pentazocine were given to groups E, F, G and H respectively. Fifteen minutes later yohimbine was given to each group intramuscularly. Dosage of yohimbine used were 0.25 mg/kg to groups E, G and H and 2 mg/kg for the group F. The groups E, F, G and H were designated as (K-Y), (K-K-Y), (B-K-Y) and (P-K-Y) respectively.

III.3.B.a. Preparation of yohimbine solution.

A 10 mg/ml solution of yohimbine[6] HCl was prepared by adding yohimbine powder to sterile water heated and stirred. using a glass rod, the mixture was not allowed to boil, but

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6. Yohimbine - Yohimbine hydrochloride - Sigma Chemical Company, P.O. Box 14508, St. Louis, MO 63178, USA.

heated until the powder dissolved (Jacobson et al., 1985).

III.3.C. Main items of observation.

Parameters recorded were temperature, pulse, respiration, haematology, regaining of pedal reflex, regaining of sternal recumbency time and complete recovery time. The methodology is same as in the second part of the experiment. The effect of yohimbine on blood pressure was studied with the help of kymograph.

III.3.D. Statistical analysis.

Statistical analysis using the CRD for assessing within group differences and student's 't' test for comparison of this groups with the groups in the second part of the experiment.

CHAPTER IV

Results

RESULTS

Data obtained during the course of investigation are presented in tables 1 to 30.

IV.1.A.a. ED_{50} of buprenorphine in rats

The ED_{50} of buprenorphine in rats (tail flick method) intraperitoneally was found to be 0.25 ± 0.084 mg/kg (Table 1 and Fig.1). The duration of analgesia was 3 to 5 h.

IV.1.A.b. ED_{50} of pentazocine in rats

The results obtained by rat tail flick method indicated that the ED_{50} of pentazocine was 32.60 ± 0.071 mg/kg body weight intraperitoneally (Table 2 and Fig.2). The duration of analgesia was 2 to 3 h.

IV.1.A.c. ED_{50} of xylazine (for analgesia) in rats

The ED_{50} of xylazine for analgesia was 1.424 ± 0.229 mg/kg intraperitoneally (Table 3 and Fig.3). The duration of analgesia was 30 to 45 min.

IV.1.B.a. ED_{50} of buprenorphine in mice

The ED_{50} of buprenorphine in mice (tail clip method) was found to be 0.9827 ± 0.0751 mg/kg intraperitoneally (Table 4 and Fig.4).

IV.1.B.b. ED_{50} of pentazocine in mice

The results obtained by mice tail clip method showed that the ED_{50} of pentazocine in mice was 48.50 ± 0.323 mg/kg intraperitoneally (Table 5 and Fig.5).

IV.1.B.c. ED_{50} of xylazine (for analgesia) in mice

The ED_{50} of xylazine for analgesia (tail clip method) in mice was found to be 7.523 ± 0.047 mg/kg intraperitoneally (Table 6 and Fig.6).

In the second part of the experiment the influence of buprenorphine, pentazocine and xylazine analgesia on ketamine anaesthesia in dogs was studied.

IV.2.A. Average body weight of the animals used were 11.41 ± 1.19 kg, 9.83 ± 1.13 kg, 12.41 ± 1.11 kg and 10.92 ± 0.95 kg in the groups A(K), B(X-K), C(B-K) and D(P-K) respectively (Tables 7, 10, 13 and 16).

IV.2.A. The drugs were administered to each group as described in materials and methods. No untoward reactions during injection could be observed.

IV.2.C.a. Sternal recumbency time

Average sternal recumbency time was 4.33 ± 1.20 min., 4.17 ± 1.2 min., 4.67 ± 0.61 min. and 4.67 ± 1.2 min respectively in groups A(K), B(X-K), C(B-K) and D(P-K) (Tables 7, 10, 13 and 16 and Fig.15).

IV.2.C.b. Clinical signs

There was catalepsy, rigidity of the head and neck, salivation, open eyelids, and fixed stare in group A(K). After xylazine administration all the animals vomited in 3 to 5 min. Pedal reflex lost in 7.33 ± 1.20 min. The

group C(B-K) and D(P-K) showed salivation. There was sedation and sleepy appearance after buprenorphine administration. The ketamine induced convulsions were absent in group C(B-K). In group D(P-K), there was salivation, licking movements, panting, excitement and staring look. All the animals in this group were producing whining noise.

There was significant reduction ($P<0.05$) in rectal temperature at 45 and 60 min. in group A(K) and became normal at 75 min. The group B(X-K), C(B-K) and D(P-K) also showed significant reduction ($P<0.05$) in rectal temperature (Tables 8, 11, 14 and 17 and Fig.7, 8, 9 and 10).

There was significant increase ($P<0.05$) in pulse rate observed in group A(K), while the pulse rate showed a significant decrease ($P<0.05$) in group B(X-K). A transient increase in pulse rate followed by decrease was observed in group C(B-K) and D(P-K) (Tables 8, 11, 14 and 17 and Fig. 7, 8, 9 and 10).

The respiration rate (per min.) showed a significant reduction in group A(K), B(X-K) and C(B-K), while the group D (P-K) showed no variations. The respiration became shallow and rapid during recovery in groups A(K), C(B-K) and D(P-K) and hence could not be recorded (Tables 8, 11, 14 and 17 and Fig. 7, 8, 9 and 10).

IV.2.C.c. Duration of anaesthesia

Average duration of anaesthesia was 45.67 $\pm$ 3.67 min. in group A(K), 79.83 $\pm$ 2.45 min. in group B(X-K), 42 $\pm$ 4.39 min.

in group C(B-K) and 29.5 ± 4.22 min. in group D(P-K) (Tables 7, 10, 13 and 16 and Fig. 15).

IV.2.C.d. Regaining of sternal recumbency

Regaining of sternal recumbency time was 50 ± 2.89 min., 83.83 ± 5.29 min., 46.67 ± 4.21 min. and 34.17 ± 3.82 min. in groups A(K), B(X-K), C(B-K) and D(P-K) respectively (Tables 7, 10, 13 and 16).

IV.2.C.e. Mean standing time

Mean standing time was 72 ± 6.98 min. in group A(K), 106.17 ± 7.0 min. in group B(X-K), 68.33 ± 2.47 min. in group C(B-K) and 62.5 ± 3.82 min. in group D(P-K) (Tables 7, 10, 13 and 16).

IV.2.C.f. Total recovery time

The total recovery time was 99.17 ± 17.58 min., 161.67 ± 11.00 min., 265.83 ± 24.10 min. and 84.17 ± 3.96 min. in groups A(K), B(X-K), C(B-K) and D(P-K) respectively (Tables 7, 10, 13 and 16 and Fig. 15).

IV.2.C.g. Haemogram

The haemoglobin (g/dl) showed a significant reduction ($P<0.05$) in group A(K) and B(X-K), but there was no significant variations in group C(B-K) and D(P-K) (Tables 9, 12, 15 and 18).

The packed cell volume (%) also showed a significant reduction ($P<0.05$) in group A(K) and B(X-K), while there was

no variations observed in group C(B-K) and D(P-K) (Tables 9, 12, 15 and 18).

The erythrocyte count ($10^6/mm^3$) showed slight reduction in group A(K) and B(X-K) while slight increase was noticed in group C(B-K) and D(P-K) (Tables 9, 12, 15 and 18).

The total leucocyte count ($10^3/mm^3$) was significantly decreased in group A(K) and B(X-K), but there was no variations observed in group C(B-K) and D(P-K) (Tables 9, 12, 15 and 18).

The results of the differential leucocyte count are presented in tables 9, 12, 15 and 18. Only the group D(P-K) exhibited significant variations in differential leucocyte count.

In the third part of the experiment reversal of anaesthesia using yohimbine was studied.

IV.3.A. Average body weight of the animals used were 14 $\pm$ 2.26 kg, 12.58 $\pm$ 0.84 kg, 13 $\pm$ 1.59 kg and 11.75 $\pm$ 1.22 kg in the groups E(K-Y), F(X-K-Y), G(B-K-Y) and H(P-K-Y) respectively (Tables 19, 22, 25 and 28).

IV.3.B. The drugs were administered to the groups E(K-Y), F(X-K-Y), G(B-K-Y) and D(P-K-Y) as described in the materials and methods. No untoward effects during administration of the drug could be observed.

IV.3.C.a. Sternal recumbency time

Average sternal recumbency time was 4 $\pm$ 1.26 min.,

2.17 ± 0.40 min., 4.33 ± 0.49 min. and 5.33 ± 0.99 min. in groups E(K-Y), F(X-K-Y), G(B-K-Y) and H(P-K-Y) respectively (Tables 19, 22, 25 and 28 and Fig.15).

IV.3.C.b. Clinical signs

All the animals produced salivation, convulsive movements, panting type of respiration and excitement and hyperaesthesia during recovery. No variations in rectal temperature could be observed. The pulse rate and respiration rate showed a significant increase ($P < 0.05$) by all the groups (Tables 20, 23, 26 and 29 and Fig. 11, 12, 13 and 14).

IV.3.C.c. Duration of anaesthesia

Average duration of anaesthesia was 34.33 ± 1.65 min., 17 ± 1.15 min., 35.67 ± 4.57 min. and 35 ± 5.79 min. in groups E(K-Y), F(X-K-Y), G(B-K-Y) and H(P-K-Y) respectively (Tables 19, 22, 25 and 28 and Fig. 15).

IV.3.C.d. Regaining of sternal recumbency time

Regaining of sternal recumbency time was 38.33 ± 1.67 min. in group E(K-Y), 39.17 ± 2.33 min. in group F(X-K-Y), 40.83 ± 4.72 min in group G(B-K-Y) and 40.33 ± 5.14 min in group H (P-K-Y) (Tables 19, 22, 25 and 28)

IV.3.C.e. Mean standing time

Mean standing time was 109.17 ± 17.58 min., 82.5 ± 12.09 min 59.33 ± 4.77 min. and 90.33 ± 6.31 min. in groups E(K-Y), F(X-K-Y), G(B-K-Y) and H(P-K-Y) respectively (Tables 19, 22, 25 and 28).

IV.3.C.f. Total recovery time

Mean total recovery time was 138.33 ± 18.33 min. in group E(K-Y), 102.5 ± 11.88 min in group F(X-K-Y), 75.83 ± 7.12 min. in group G(B-K-Y) and 129.17 ± 5.54 min in group H (P-K-Y) (Tables 19, 22, 25 and 28 and Fig. 18).

IV.3.C.g. Haemogram

There was no variation in haemoglobin, packed cell volume and total erythrocyte count. The total leucocyte count showed a slight increase by all the groups. The differential leucocyte count did not show much variations (Tables 21, 24, 27 and 30).

COMPARISON OF GROUPS A, B, C, D, WITH GROUPS E, F, G, H.

IV.4.A. Comparison between group A and group E.

Sternal recumbency during onset 4.33 ± 1.20 min. and 4 ± 1.26 min. in groups A and E respectively (Fig.15).

A significant reduction in rectal temperature noticed at 45 and 60 min. in group A, while there was no significant variation noticed in group E.

A significant increase in pulse rate noticed throughout the experiment in group A and group E.

A significant decrease in respiration rate was noticed at 30 min. in group A, while there was no variations in respiration rate noticed in group E.

Duration of anaesthesia was 45.67 ± 3.67 min. and 34.33 ± 1.65 min. in group A and E respectively. There was slight reduction in duration of anaesthesia in group E (Fig. 15).

Time taken for regaining sternal recurbency was 50 ± 2.89 min. in group A and 38.33 ± 1.67 min. in group E. There was significant reduction in regaining of sternal recumbency time in group E.

Standing time was 72 ± 6.98 min in group A and 109.17 ± 17.58 min. in group E. There was slight increase in standing time noticed.

Total recovery time was 138.33 ± 18.33 min. in group A and 99.17 ± 17.58 min in group E. Prolongation of total recovery time noticed in group E (Fig. 15).

A significant decrease in haemoglobin content was noticed in group A, while there was no variations in haemoglobin content in group B.

A slight reduction in packed cell volume, and total erythrocyte count in group A, while there was a slight increase noticed in both the parameters in group B.

Total leucocyte count also showed a tendency to decrease in group A, but a slight increase noticed in group B.

A slight increase in neutrophil count and decrease in lymphocyte count noticed in group A, but there was no variations observed in the above two parameters in group B.

No variations in eosinophil count noticed in group A and B.

IV.4.B. Comparison between group E and F.

The animals attained sternal recumbency at 4.17 ± 1.25 min. in group E and 2.17 ± 0.40 min. in group F (Fig.15).

There was a significant reduction in rectal temperature at 45, 60, 75, 90 and 120 min. in group E, while there was no significant variations noticed in the group F.

There was a significant reduction in pulse rate noticed throughout the anaesthesia in group E, but, there was a significant increase noticed in group F.

Respiration rate per min. significantly decreased at 5, 10, 15, 30 and 45 min. in group E, but there was a slight increase noticed after yohimbine administration in group F.

The duration of anaesthesia was 46.83 ± 5.00 min. in group B and 22.67 ± 0.71 min in group F. A statistically significant ($P < 0.05$) reduction in duration of anaesthesia was noticed in group F (Fig. 15).

The regaining of sternal recumbency time was 83.83 ± 5.29 min. in group B and 39.17 ± 2.39 min. in group F. A significant ($P < 0.05$) reduction was observed in group F.

The standing time was 106.17 ± 7.00 min. in group B and 82.5 ± 12.09 min. in group F. There was slight reduction in standing time in the group F.

The total recovery time was 161.67 ± 11.00 min. and 102.5 ± 11.88 min. in group B and F respectively. There was a significant reduction ($P < 0.05$) noticed in group F (Fig. 15).

The haemoglobin content showed a slight decrease at 30 min. in group B, while such a decrease is also shown by the group F, eventhough with a slight improvement.

The packed cell volume also decreased at 30 min. in group B, but there was a very slight decrease noticed in group F.

The total erythrocyte count showed a slight decrease at 30 min. in group B. The group F also showed a slight decrease.

The total leucocyte count decreased considerably in group B, but, it increased slightly in group F.

There was no variations in neutrophil count, in group B, while there was slight increase noticed in group F. There was

no variations in lymphocyte count in group B, while there was slight reduction in lymphocyte count noticed at 30 min.

There was no variations in eosinophil count in group B and F.

IV.4.C. Comparison between group C and group G.

The average sternal recumbency time was 4.67 ± 0.61 min. in group C and 4.33 ± 0.49 min. in group G (Fig. 15).

The rectal temperature showed a significant decrease ($P<0.05$) from 75 to 180 min. onwards in group C, but there was no variation in rectal temperature noticed in group G.

The pulse rate showed no variation in group C, while a significant increase ($P<0.05$) noticed at 30, 45 and 60 min. in the group G.

A significant decrease ($P<0.05$) in respiration rate noticed in group G, while there was a significant increase in respiration rate after yohimbine administration.

The duration of anaesthesia was 42 ± 4.39 min. in group C and 35.67 ± 4.57 min in group G. There was a slight reduction noticed in group G (Fig. 15).

The time for regaining sternal recumbency was 46.67 ± 4.21 min. in group C and 40.83 ± 4.72 min. in group G. There was a slight reduction noticed in group G.

The standing time was 68.33 ± 2.47 min. in group C and 58.33 ± 4.77 min. in group G. A slight reduction in standing time was noticed in group G.

The total recovery time was 265.83 ± 24.10 min. in group C and 75.83 ± 7.12 min. in group G. There was a significant reduction ($P < 0.05$) noticed in group G (Fig. 15).

A slight decrease in haemoglobin content noticed at 30 min. in group C, while there was an increase in haemoglobin content noticed in group G.

There was a slight decrease in packed cell volume noticed at 30 min. in group C, while there was considerable increase in packed cell volume in group G.

There was no significant variation in total erythrocyte count observed in group C as well as in group G.

The total leucocyte count also showed no variations in the group C as well as in the group G.

The neutrophil count showed a significant decrease ($P < 0.05$) at 30 min. in group C, but there was no variations noticed in group G.

The lymphocyte count showed a significant increase ($P < 0.05$) at 30 min. in group C, but there was no variations observed in group G.

There was no variations in eosinophil count observed in group C as well as in the group G.

IV.4.D. Comparison between the group D and H.

The sternal recumbency time was 4.67 ± 1.28 min. in the group D and 5.33 ± 0.99 min. in the group H (Fig. 19).

The rectal temperature showed a significant increase at 90, 120, 150 and 180 min. while there was no variations noticed in the group H.

The pulse rate per min. showed no variations in the group D, while there was significant increase ($P < 0.05$) in pulse rate observed after yohimbine administration.

There was no variations in the respiration rate in the group D, but there was significant increase ($P < 0.05$) noticed after yohimbine administration.

The duration of anaesthesia was 29.5 $\pm$ 4.22 min. in the group D and 38 $\pm$ 5.79 min. in the group H. There was a slight increase in the duration of the anaesthesia in the group H (Fig. 15).

The time for regaining of the sternal recumbency was 34.17 $\pm$ 3.52 min. in the group D and 40.33 $\pm$ 5.14 min. in the group H.

The standing time was 62.5 $\pm$ 3.62 min. in the group D and 90.33 $\pm$ 6.31 min. in the group H. There was significant increase ($P < 0.05$) in standing time observed in group H.

The total recovery time was 84.17 $\pm$ 3.96 min. in the group D and 129.17 $\pm$ 5.54 min. in the group H. There was a significant increase ($P < 0.05$) in total recovery time noticed in the group H (Fig. 15).

There was no variations in haemoglobin content observed in group D as well as in group H.

The packed cell volume showed a slight increase at 30 min. in the group D as well as group H.

There was no variation in the total erythrocyte count in both the groups (D and H).

The total leucocyte count also showed no variation in the group D and H.

The neutrophil count showed a significant decrease ($P < 0.05$) at 30 min. in the group D, while there was no variation noticed in the group H.

The lymphocyte count showed a significant increase ($P < 0.05$) at 30 min. in the group D, while there was no significant variation noticed in the group H.

There was no variations in eosinophil count noticed in the group D as well as in the group H.

Tables

Table 1. ED_{50} of buprenorphine in rats

Dose	Log dose	Number of animals	Positive response	Negative response	Cumulative positive response	Cumulative negative response	Total	Percentage of cumulative response
0.03875	$\bar{2}.5883$	10	0	10	0	28	28	0
0.0675	$\bar{2}.8293$	10	3	7	3	18	21	10.71
0.125	$\bar{1}.0969$	10	5	5	8	11	19	28.57
0.25	$\bar{1}.3979$	10	6	4	14	6	20	50
0.5	$\bar{1}.6990$	10	8	2	22	2	24	78.57
0.75	$\bar{1}.8751$	10	10	0	32	0	32	114.29

ED_{50} of buprenorphine in rats = 0.25 $\pm$ 0.084 mg/kg body weight

Table 2. ED_{50} of pentazocine in rats

Dose	Log dose	Number of animals	Positive response	Negative response	Cumulative positive response	Cumulative negative response	Total	Percentage of cumulative response
15	1.1761	10	0	10	0	31	31	0
20	1.3010	10	2	8	2	21	23	6.45
25	1.3979	10	4	6	6	13	19	19.35
30	1.4771	10	5	5	11	7	18	35.48
35	1.5441	10	8	2	19	2	21	61.29
40	1.6021	10	10	0	29	0	29	93.54

ED_{50} of pentazocine in rats = 32.60 $\pm$ 0.071 mg/kg body weight

Table 3. ED_{50} of xylazine in rats

Dose	Log dose	Number of animals	Positive response	Negative response	Cumulative positive response	Cumulative negative response	Total	Percentage of cumulative response
0.25	$\bar{1}$.3979	10	0	10	0	24	24	0
0.5	$\bar{1}$.6990	10	3	7	3	14	17	12.5
1	0.0000	10	5	5	8	7	15	33.33
2	0.3010	10	8	2	16	2	18	66.66
3	0.4771	10	10	0	26	0	26	108.33

ED_{50} of xylazine in rats = 1.424 $\pm$ 0.229 mg/kg body weight

Table 4. ED_{50} of buprenorphine in mice

Dose	Log dose	Number of animals	Positive response	Negative response	Cumulative positive response	Cumulative negative response	Total	Percentage of cumulative response
0.25	$\bar{1}.3979$	10	0	10	0	25	25	0
0.5	$\bar{1}.6990$	10	2	8	2	15	17	8
0.75	$\bar{1}.8751$	10	5	5	7	7	14	28
1	0.0000	10	8	2	15	2	17	60
1.5	0.1761	10	10	0	25	0	25	100

ED_{50} of buprenorphine in mice = 0.9827 $\pm$ 0.0751 mg/kg body weight

Table 5. ED_{50} of pentazocine in mice

Dose	Log dose	Number of animals	Positive response	Negative response	Cumulative positive response	Cumulative negative response	Total	Percentage of cumulative response
20	1.3010	10	0	10	0	32	32	0
30	1.4771	10	2	8	2	22	24	6.25
40	1.6021	10	4	6	6	14	20	18.75
45	1.6532	10	5	5	11	8	19	34.38
50	1.6990	10	7	3	18	3	21	56.25
60	1.7782	10	10	0	28	0	28	87.5

ED_{50} of pentazocine in mice = 48.50 $\pm$ 0.323 mg/kg body weight

Table 6. ED_{50} of xylazine in mice

Dose	Log dose	Number of animals	Positive response	Negative response	Cumulative positive response	Cumulative negative response	Total	Percentage of cumulative response
2	0.3010	10	0	10	0	27	27	0
4	0.6021	10	3	7	3	17	20	11
6	0.7782	10	5	5	8	10	18	29.63
8	0.9031	10	7	3	15	5	20	55.55
10	1.0000	10	8	2	23	2	25	85.19
12	1.0792	10	10	0	33	0	33	122.22

ED_{50} of xylazine in mice = 7.523 ± 0.047 mg/kg body weight

Table 7. Effect of intramuscular administration of ketamine (20 mg/kg) in Dogs. Sternal recumbency, duration of anaesthesia, regaining of sternal recumbency, standing time and total recovery time

Animal No.	Body weight (kg)	Sternal recumbency (min.)	Duration of anaesthesia (min.)	Regaining of sternal recumbency (min.)	Standing time (min.)	Total recovery time (min.)	Other observations
A1	8	10	35	45	65	80	Shivering of head and neck region. Rigidity of the muscles of head and neck. Head turned to one side. Licking movements. All the reflexes present. Staring look. Convulsive movement in two animals. Profuse salivation. Curling of the tongue
A2	10	3	47	50	67	90	
A3	15	3	57	60	105	135	
A4	15	5	35	40	60	70	
A5	10	2	48	50	60	100	
A6	10.5	3	52	55	75	120	
Mean ±S.E.	11.41 ±1.19	4.33 ±1.20	45.67 ±3.67	50 ±2.89	72 ±6.98	99.17 ±17.53	

Table 8. Effect of intramuscular administration of ketamine (20 mg/kg) in Dogs: Temperature, pulse and respiration (Mean ± S.D.), n = 6

Parameters and units	Intervals (minutes)									
	0	5	10	15	30	45	60	75	90	120
Temperature (°F)	101.77 ±0.20	101.82 ±0.09	101.53 ±0.13	101.27 ±0.18	101.1 ±0.36	100.6* ±0.28	100.77* ±0.26	101.53 ±0.39	101.73 ±0.14	102.07 ±0.17
Pulse/min.	99.67 ±8.30	131.33* ±6.30	134* ±7.85	125.33* ±7.89	144.67* ±3.92	141* ±4.84	137* ±9.10	133* ±8.76	121.33* ±6.0	116.5 ±0.23
Respiration/min.	32.33 ±2.55	26.33 ±1.96	24 ±2.58	24* ±3.39	-	-	-	-	-	-

* Significant at 5% level

Table 9. Effect of intramuscular administration of ketamine (20 mg/kg) in Dogs: Haemogram
(Mean ± S.E.), n = 6

Parameters and units	Intervals		
	0	30 min.	24 h
Haemoglobin (g/dl)	15 ± 0.82	12.5 ± 0.43*	15 ± 0.86
Packed cell volume (%)	46 ± 2.74	39.66 ± 2.17*	45.66 ± 2.69
Total erythrocyte count ($10^6/mm^3$)	8.06 ± 0.48	6.42 ± 0.44	7.86 ± 0.53
Total leucocyte count ($10^3/mm^3$)	15.63 ± 0.54	12.06 ± 1.13*	14.63 ± 0.52
Neutrophil (%)	64.33 ± 3.04	69.5 ± 2.72	64.33 ± 2.91
Lymphocyte (%)	30.33 ± 2.33	25.17 ± 1.89	29.67 ± 2.59
Eosinophil (%)	5 ± 0.89	5.33 ± 1.04	6 ± 0.58

* Significant at 5 % level

Table 10. Effect of intramuscular administration of Ketamine (15 mg/kg) and xylazine (2 mg/kg) in Dogs: Sternal recumbency, duration of anaesthesia, regaining of sternal recumbency, standing time and total recovery time

Animal No.	Body weight (Kg)	Sternal recumbency (min.)	Duration of anaesthesia (min.)	Regaining of sternal recumbency (min.)	Standing time (min.)	Total recovery time (min.)	Other observations
B1	8.5	2	78	80	105	180	All the animals vomited within 3-5 min. after xylazine administration. Palpabral and corneal reflex persist. Pedal reflex lost in 7.33 ± 1.20 minutes. One animal showed excitement during recovery.
B2	8	3	73	75	85	120	
B3	8.5	5	95	100	130	175	
B4	8	2	68	70	90	180	
B5	15	3	97	100	120	135	
B6	11	10	68	78	107	180	
Mean ± S.E.	9.83 ±1.13	4.17 ±1.25	79.83 ±2.45	83.83 ±5.29	106.17 ±7.00	161.67 ±11.00	

Table 11. Effect of intramuscular administration of ketamine (15 mg/kg) and xylazine (2 mg/kg) in Dogs: Temperature, pulse and respiration (Mean ± S.E.), n = 6

Parameters and units	Intervals (minutes)									
	0	5	10	15	30	45	60	75	90	120
Temperature (°F)	102.67 ±0.14	102.47 ±0.28	102.1 ±0.21	102 ±0.27	101.77 ±0.22	100.87* ±0.36	100.5* ±0.39	99.72* ±0.47	99.53* ±0.42	97.63* ±1.65
Pulse/min.	120.33 ±2.16	88.33* ±6.10	92* ±4.62	91.67* ±6.44	89.33* ±6.61	79.17* ±5.65	76.83* ±5.21	81.67* ±5.83	77.67* ±5.43	76.67* ±6.1
Respiration/min.	34.33 ±4.1	18.67* ±3.85	13* ±4.09	10.66* ±1.74	11.5* ±1.86	23.66* ±2.59	28* ±4.62	33.83 ±4.53	35.66 ±3.81	32.67 ±4.18

* Significant at 5% level

Table 12. Effect of intramuscular administration of ketamine (15 mg/kg) and xylazine (2 mg/kg) in Dogs: Haemogram

(Mean ± S.E.), n = 6

Parameters and units	Interval		
	0	30 min	24 h
Haemoglobin (g/dl)	15.08 ± 1.08	12.83 ± 0.81*	14.75 ± 1.09
Packed cell volume (%)	46.5 ± 2.64	38.17 ± 2.99*	45.83 ± 2.75
Total erythrocyte count (10^6/mm^3)	7.89 ± 0.52	6.27 ± 0.33	7.69 ± 0.51
Total leucocyte count (10^3/mm^3)	16.07 ± 1.39	12.68 ± 1.61*	15.95 ± 1.75
Neutrophil (%)	67.83 ± 2.52	66.33 ± 1.52	68.5 ± 3.22
Lymphocyte (%)	25.67 ± 1.99	27.17 ± 1.50	26.83 ± 2.82
Eosinophil (%)	6.5 ± 0.89	6.5 ± 1.12	4.67 ± 1.02

* Significant at 5% level

Table 13. Effect of intramuscular administration of ketamine (15 mg/kg) and buprenorphine (0.03 mg/kg) in Dogs: Sternal recumbency, duration of anaesthesia, regaining of sternal recumbency, standing time and total recovery time

Animal No.	Body weight (kg)	Sternal recumbency (min.)	Duration of anaesthesia (min.)	Regaining of sternal recumbency	Standing time (min.)	Total recovery time (min.)	Other observations
B1	10	3	52	55	70	240	Salivation started in about 3 to 10 min. in all animals after buprenorphine administration. Respiration became panting. Tremors and convulsions absent. All the reflexes were persisting. Sedation, sleepy appearance and drooping of head after buprenorphine. Sleep for 3 to 5 hours.
B2	15	5	40	45	65	315	
B3	10	5	55	60	75	210	
B4	12	7	32	45	75	220	
B5	16.5	5	25	30	60	360	
B6	11	3	42	45	65	250	
Mean ± S.E.	12.41 ±1.11	4.67 ±0.61	42 ±4.39	46.67 ±4.21	69.33 ±2.47	265.83 ±24.10	

Table 14. Effect of intramuscular administration of ketamine (15 mg/kg) and buprenorphine (0.03 mg/kg) in Dogs
Temperature, pulse and respiration
(Mean ± S.E.), n = 6

Parameters and units	Intervals (minutes)												
	0	5	10	15	30	45	60	75	90	105	120	150	180
Temperature (°F)	101.67 ±0.36	100.67 ±0.30	100.5 ±0.30	100.7 ±0.27	101 ±0.40	101.03 ±0.40	100.9 ±0.36	100.4* ±0.47	100.13* ±0.44	99.33* ±0.48	99.07* ±0.41	99.32* ±0.49	99.57* ±0.49
Pulse/min	97.33 ±5.74	103 ±6.63	116.33 ±9.36	106 ±8.78	105 ±8.24	85.5 ±6.88	92.67 ±8.56	95.67 ±7.56	92 ±8.70	83.33 ±4.99	84.67 ±5.63	81.66 ±8.88	79.83 ±8.81
Respiration/min.	46 ±3.06	29* ±1.77	28.67* ±2.35	27.67* ±2.60	36.67* ±4.09	33.33* ±3.17	-	-	-	-	-	-	-

* Significant at 5% level

Table 15. Effect of intramuscular administration of ketamine (15 mg/kg) and buprenorphine (0.03 mg/kg) in Dogs: Haemogram (Mean ± S.E.), n = 6

Parameters and units	Interval		
	0	30 min.	24 h
Haemoglobin (g/dl)	15.25 ± 0.70	14.33 ± 0.85	15.17 ± 0.53
Packed cell volume (%)	44.33 ± 1.76	42.5 ± 2.54	44.17 ± 1.19
Total erythrocyte count ($10^6/mm^3$)	7.65 ± 0.38	7.44 ± 0.32	7.38 ± 0.37
Total leucocyte count ($10^3/mm^3$)	9.90 ± 0.70	9.47 ± 0.95	11.09 ± 0.74
Neutrophil (%)	68.83 ± 1.74	58.50 ± 0.76*	66.5 ± 1.67
Lymphocyte (%)	24.17 ± 2.21	35 ± 0.63*	27.83 ± 1.45
Eosinophil (%)	7 ± 0.97	6.5 ± 0.67	5.67 ± 0.33

* Significant at 5% level

Table 16. Effect of intramuscular administration of ketamine (15 mg/kg) and pentazocine (2 mg/kg) in Dogs: Sternal recumbency, duration of anaesthesia, regaining of sternal recumbency, standing time and total recovery time

Animal No.	Body weight (kg)	Sternal recumbency (min.)	Duration of anaesthesia (min.)	Regaining of sternal recumbency (min.)	Standing time (min.)	Total recovery time (min.)	Other observations
D1	10	10	25	30	70	85	10 to 15 min. after pentazocine administration salivation started, convulsive movements, licking movements, panting type of respiration. One animal vomited. The vomitus consists of froth and mucus. Excitement and staring look. All the animals were crying throughout.
D2	8	3	27	30	60	90	
D3	10	3	22	25	50	90	
D4	11.5	2	43	45	65	85	
D5	11	7	23	30	55	65	
D6	15	3	42	45	75	90	
Mean ± S.E.	10.92 ±0.95	4.67 ±1.28	29.5 ±4.22	34.17 ±3.52	62.5 ±3.82	84.17 ±3.96	

Table 17. Effect of intramuscular administration of ketamine (15 mg/kg) and pentazocine (2 mg/kg) in Dogs· Temperature, pulse and respiration (Mean ± S.E.), n = 6.

Parameters and units	Intervals (minutes)											
	0	5	10	15	30	45	60	75	90	120	150	180
Temperature (°F)	101.67 ±3.6	100.65 ±0.29	100.7 ±0.40	100.63 ±0.25	100.7 ±0.25	101.03 ±0.38	100.63 ±0.53	100.03 ±0.51	99.3* ±0.58	98.98* ±0.46	99.35* ±0.53	99.63* ±0.56
Pulse/min.	97.33 ±5.74	98.33 ±4.36	119.67 ±9.36	107.33 ±8.70	104.33 ±7.82	92 ±8.33	93.67 ±9.01	100.33 ±7.91	88.33 ±9.39	90.33 ±7.79	86.16 ±8.36	78.17 ±7.76
Respiration/min.	35 ±2.91	36.67 ±3.17	35.33 ±2.81	35 ±1.24	35.67 ±2.55	-	-	-	-	-	-	-

* Significant at 5% level

Table 18. Effect of intramuscular administration of ketamine (15 mg/kg) and pentazocine (2 mg/kg) in Dogs: Haemogram (Mean ± S.E.), n = 6

Parameters and units	Intervals		
	0	30 min.	24 h
Haemoglobin (g/dl)	13.75 ± 0.91	15 ± 0.92	14.33 ± 0.92
Packed cell volume (%)	41.17 ± 3.32	44.33 ± 3.08	43.08 ± 2.81
Total erythrocyte count ($10^6/mm^3$)	6.95 ± 0.39	7.50 ± 0.35	7.29 ± 0.34
Total leucocyte count ($10^3/mm^3$)	13.43 ± 2.08	14.2 ± 1.97	12.42 ± 2.02
Neutrophil (%)	68.33 ± 2.97	58.17 ± 0.87*	70.17 ± 2.66
Lymphocyte (%)	27.17 ± 2.21	37.5 ± 0.81*	25.33 ± 2.73
Eosinophil (%)	4.5 ± 1.02	4.33 ± 0.56	4.83 ± 0.60

* Significant at 5% level

Table 19. Effect of intramuscular administration of ketamine (20 mg/kg) and yohimbine (0.25 mg/kg) in Dogs: Sternal recumbency, duration of anaesthesia, regaining of sternal recumbency, standing time and total recovery time

Animal No.	Body weight (kg)	Sternal recumbency (min.)	Duration of anaesthesia (min.)	Regaining of sternal recumbency (min.)	Standing time (min.)	Total recovery time (min.)	Other observations
E1	23	1	34	35	165	190	Salivation, convulsive movements, one animal vomited, panting type of respiration hyperaesthesia.
E2	10	4	41	45	160	190	
E3	9	3	32	35	70	90	
E4	18	3	37	40	80	100	
E5	14	3	32	35	105	150	
E6	10	10	30	40	75	110	
Mean ± S.E.	14 ±2.26	4 ±1.26	34.33 ±1.65	38.33 ±1.67	109.17 ±17.58	138.33 ±18.33	

Table 20. Effect of intramuscular administration of ketamine (20 mg/kg) and yohimbine (0.25 mg/kg) in Dogs: Temperature, pulse and respiration (Mean ± S.E.), n =6

Parameters and units	Intervals (min.)									
	0	5	10	15	30	45	60	75	90	120
Temperature (°F)	102.07 ±0.28	102.07 ±0.63	102.17 ±0.63	102.27 ±0.60	102.07 ±0.65	102.50 ±0.53	103.23 ±0.63	102.87 ±0.52	103 ±0.48	102 ±0.24
Pulse/min.	123 ±10.2	142.7 ±12.3	143.3 ±7.3	141.0 ±7.2	166* ±9.5	187* ±5.4	176* ±9.4	164* ±12.9	142.3 ±5.4	132.5 ±6.8
Respiration/min.	47 ±5.1	26.7 ±2.6	25.7 ±1.7	31 ±2.3	39.7 ±3.8	44 ±2.3	-	-	-	-

* Significant at 5% level

Table 21. Effect of intramuscular administration of ketamine (20 mg/kg) and yohimbine (0.25 mg/kg) in Dogs: Haemogram (Mean ± S.E.), n = 6

Parameters and units	Intervals		
	0	30 min.	24 h
Haemoglobin (g/dl)	12.33 ± 0.76	13.08 ± 0.66	13.33 ± 0.63
Packed cell volume (%)	40.17 ± 1.52	42.17 ± 1.14	41.5 ± 1.84
Total erythrocyte count ($10^6/mm^3$)	5.95 ± 0.33	6.11 ± 0.35	6.51 ± 0.46
Total leucocyte count ($10^3/mm^3$)	12.94 ± 1.10	14.01 ± 1.44	12.76 ± 0.71
Neutrophil (%)	69.17 ± 3.20	70.5 ± 2.39	67.83 ± 2.48
Lymphocyte (%)	27.5 ± 3.47	25.33 ± 2.42	28.67 ± 2.73
Eosinophil (%)	5 ± 0.93	3.83 ± 0.65	3.5 ± 0.56

Table 22. Effect of intramuscular administration of ketamine (15 mg/kg), xylazine (2 mg/kg) and yohimbine (2 mg/kg) in Dogs: Sternal recumbency, duration of anaesthesia, regaining of sternal recumbency, standing time and total recovery time

Animal No.	Body weight (kg)	Sternal recumbency (min.)	Duration of anaesthesia (min.)	Regaining of sternal recumbency (min.)	Standing time (min.)	Total recovery time (min.)	Other observations
F1	11	2	43	45	75	90	Salivation, hyperexcitement, convulsive movements, crawling on the ground, panting type of respiration
F2	13	1	36	35	45	60	
F3	13	2	38	40	65	90	
F4	10	2	28	30	75	105	
F5	16	2	43	45	110	135	
F6	12.5	4	36	40	125	135	
Mean ± S.E.	12.58 ±0.84	2.17 ±0.40	37 ±2.33	39.17 ±2.39	82.5 ±12.09	102.5 ±11.88	

Table 23. Effect of intramuscular administration of ketamine (15 mg/kg), xylazine (2 mg/kg) and yohimbine (2 mg/kg) in Dogs: Temperature, pulse and respiration (Mean ± S.E.), n = 6

Parameters and units	Intervals (min.)									
	0	5	10	15	30	45	60	75	90	120
Temperature (°F)	101.6 ±0.40	102.1 ±0.40	102.2 ±0.40	102.2 ±0.40	101.9 ±0.40	101.9 ±0.60	102.2 ±0.30	102.3 ±0.20	101.9 ±0.20	101.7 ±0.22
Pulse/min.	104 ±8.33	102 ±6.81	97.33 ±6.36	89.67 ±7.51	105.4 ±10.8	121.6 ±10.68	138.4* ±9.77	136* ±7.48	134.8* ±8.30	125.67* ±5.55
Respiration/min.	42 ±3.83	13.33 ±1.12	10.17 ±0.98	8.67 ±0.71	29 ±5.74	45 ±1.91	-	-	-	-

* Significant at 5% level

Table 24. Effect of intramuscular administration of ketamine (15 mg/kg), xylazine (2 mg/kg) and yohimbine (2 mg/kg) in Dogs: Haemogram (Mean ± S.E.), n = 6.

Parameters and units	Intervals		
	0	30 min.	24 h
Haemoglobin (g/dl)	15.08 ± 0.95	13.83 ± 0.91	16 ± 0.76
Packed cell volume (%)	43.83 ± 1.90	40.83 ± 1.83	46 ± 1.55
Total erythrocyte count ($10^6/mm^3$)	7.52 ± 0.47	6.94 ± 0.47	7.72 ± 0.45
Total leucocyte count ($10^3/mm^3$)	9.63 ± 1.28	10.32 ± 1.61	9.73 ± 0.92
Neutrophil (%)	72 ± 2.52	75.33 ± 2.23	72.17 ± 1.89
Lymphocyte (%)	24.17 ± 2.26	20.67 ± 2.89	24.83 ± 1.94
Eosinophil (%)	3.93 ± 0.54	4 ± 0.93	3.98 ± 0.68

Table 25. Effect of intramuscular administration of ketamine (15 mg/kg), buprenorphine (0.03 mg/kg) and yohimbine (0.25 mg/kg) in Dogs: Sternal recumbency, duration of anaesthesia, regaining of sternal recumbency, standing time and total recovery time

Animal No.	Body weight (kg)	Sternal recumbency (min.)	Duration of anaesthesia (min.)	Regaining of sternal recumbency (min.)	Standing time (min.)	Total recovery time (min.)	Other observations
G1	13	3	27	30	45	50	4 to 5 min. after yohimbine administration, movement of head noticed, watery salivation in all animals. Buprenorphine induced sleeping absent
G2	18	3	42	45	55	60	
G3	8	5	55	60	75	90	
G4	17	5	25	30	70	90	
G5	12	4	31	35	50	75	
G6	10	6	34	40	55	50	
Mean ± S.E.	13 ±1.59	4.33 ±0.49	40.83 ±4.72	35.67 ±4.57	58.33 ±4.77	75.83 ±7.12	

Table 26. Effect of intramuscular administration of ketamine (15 mg/kg), buprenorphine (0.03 mg/kg) and yohimbine (0.25 mg/kg) in Dogs: Temperature, pulse and respiration
(Mean ± S.E.), n = 6.

Parameters and units	Intervals (min.)								
	0	5	10	15	30	45	60	75	90
Temperature (°F)	101.1 ±0.44	100.97 ±0.52	100.87 ±0.52	100.93 ±0.43	101.1 ±0.56	101.8 ±0.51	101.8 ±0.49	101.4 ±0.45	101 ±0.40
Pulse/min.	112 ±7.50	128.33 ±9.72	120.67 ±11.66	120.3 ±11.54	150.67* ±6.53	162* ±11.85	171.67* ±10.13	147 ±16.02	121.3 ±9.79
Respiration/min.	48 ±3.97	35 ±2.62	31 ±4.02	28 ±3.72	41.67* ±4.72	48* ±3.01	-	-	-

* Significant at 5% level

Table 27. Effect of intramuscular administration of ketamine (15 mg/kg), buprenorphine (0.03 mg/kg) and yohimbine (0.25 mg/kg) in dogs: Haemogram
(Mean ± S.E.), n = 6

Parameters and units	Intervals		
	0	30 min.	24 h
Haemoglobin (g/dl)	11.42 ± 0.58	13.67 ± 0.95	12.92 ± 0.87
Packed cell volume (%)	37.5 ± 2.75	43 ± 3.78	41 ± 3.53
Total erythrocyte count ($10^6/mm^3$)	5.08 ± 0.28	5.92 ± 0.54	5.69 ± 0.48
Total leucocyte count ($10^3/mm^3$)	15.31 ± 1.73	16.38 ± 1.38	14.98 ± 1.39
Neutrophil (%)	73.67 ± 2.80	70.51 ± 2.26	72.67 ± 2.0
Lymphocyte (%)	22.03 ± 2.69	25.00 ± 2.21	24.0 ± 2.38
Eosinophil (%)	3.5 ± 0.89	4.5 ± 0.89	3.33 ± 0.49

Table 28. Effect of intramuscular administration of ketamine (15 mg/kg), pentazocine (2 mg/kg) and yohimbine (0.25 mg/kg) in Dogs: Sternal recumbency, duration of anaesthesia, regaining of sternal recumbency, standing time and total recovery time

Animal No.	Body weight (kg)	Sternal recumbency (min.)	Duration of anaesthesia (min.)	Regaining of sternal recumbency (min.)	Standing time (min.)	Total recovery time (min.)	Other observations
H1	13	5	25	30	90	120	Within 5 to 10 min. after yohimbine administration head kept raised, profuse salivation, saliva was thick and viscid, hyper-excitement, prolonged recumbency.
H2	8	10	20	30	105	130	
H3	13.5	5	22	27	77	130	
H4	15	4	46	50	110	150	
H5	13	3	52	55	70	110	
H6	13	5	45	50	90	135	
Mean ± S.E.	11.75 ±1.22	5.33 ±0.99	35 ±5.79	40.33 ±5.14	90.33 ±6.31	129.17 ±5.54	

Table 29. Effect of intramuscular administration of ketamine (15 mg/kg), pentazocine (2 mg/kg) and yohimbine (0.25 mg/kg) in Dogs: Temperature, pulse and respiration
(Mean ± S.E.), n = 6

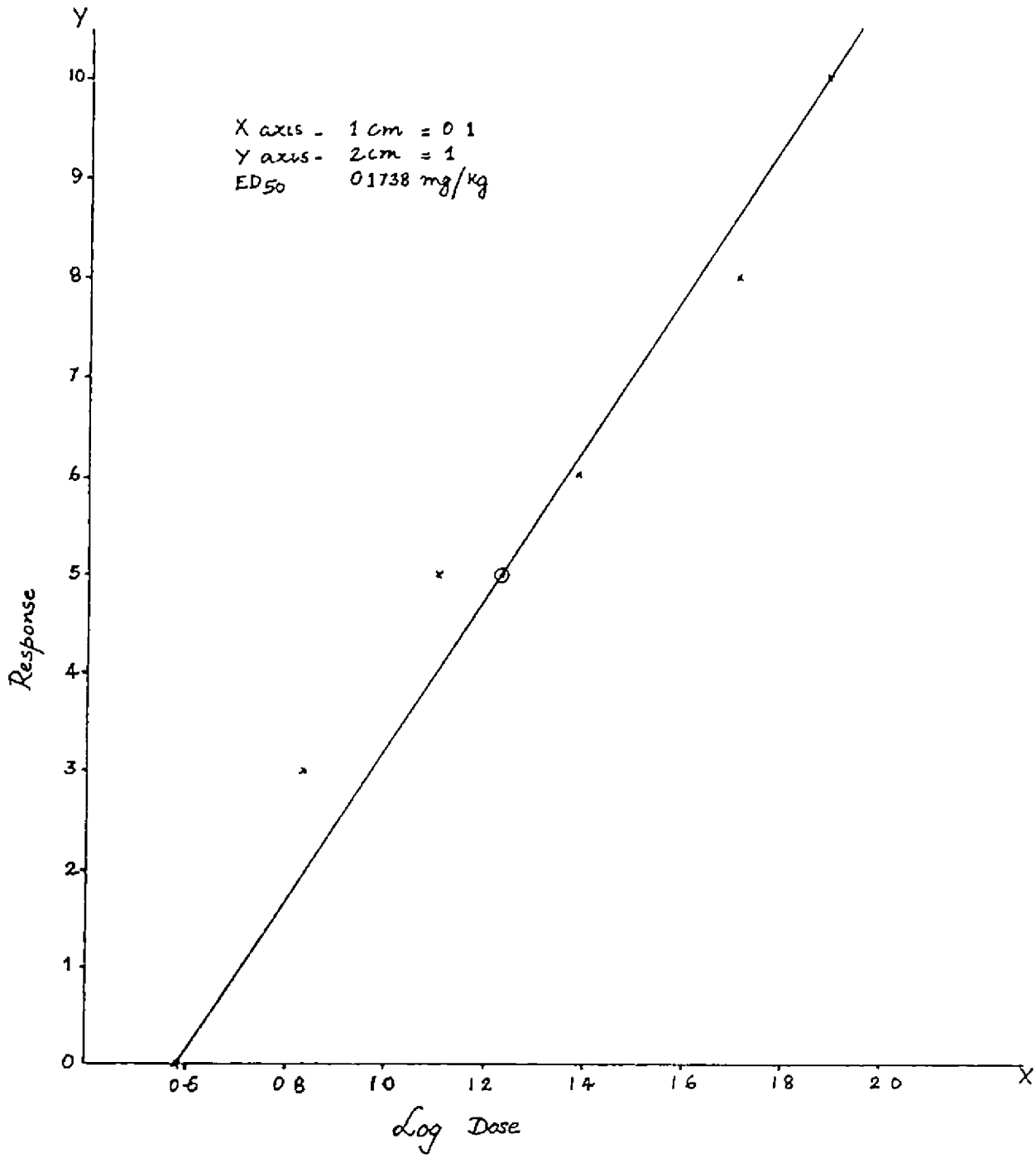
Parameters and units	Intervals (min.)								
	0	5	10	15	30	45	60	75	90
Temperature (°F)	100.4 ±0.14	100.5 ±0.18	100.43 ±0.14	100.4 ±0.21	101.03 ±0.20	101.47 ±0.23	101.7 ±0.38	101.4 ±0.33	100.67 ±0.28
Pulse/min.	99.67 ±2.44	130.67 ±7.86	154 ±10.21	157.67 ±8.86	169.33 ±8.31	167.33 ±8.01	170* ±9.18	159.67 ±10.15	134 ±6.25
Respiration/min.	47 ±4.7	37.33 ±2.17	28.67 ±1.43	29 ±2.62	41.67* ±2.55	47.33* ±2.11	-	-	-

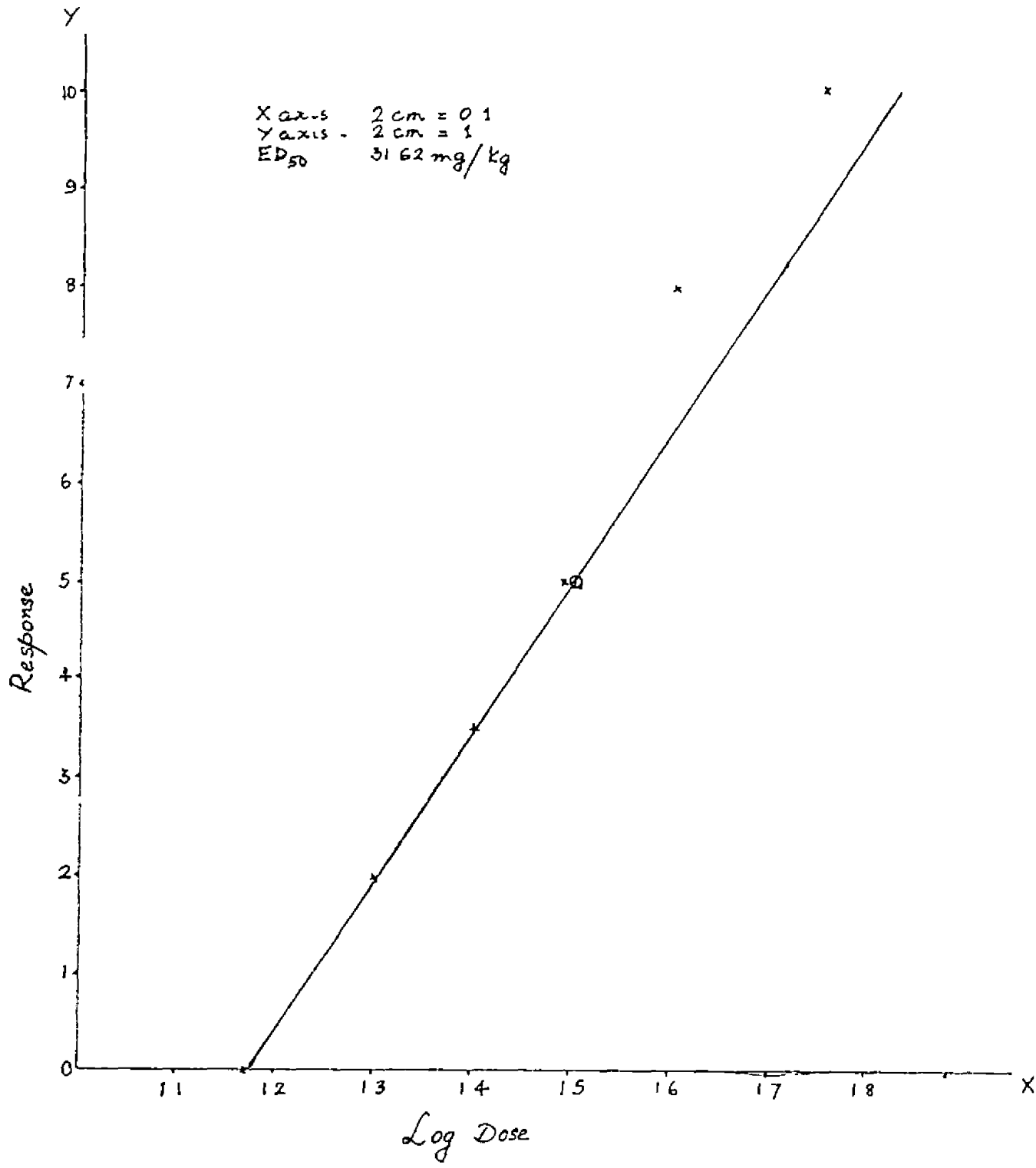
* Significant at 5% level

Table 30. Effect of intramuscular administration of ketamine (15 mg/kg), pentazocine (2 mg/kg) and yohimbine (0.25 mg/kg) in Dogs: Haemogram (Mean ± S.E.), n = 6

Parameters and units	Intervals		
	0	30 min.	24 h
Haemoglobin (g/dl)	12.42 ± 1.08	13.83 ± 1.11	13 ± 0.99
Packed cell volume (%)	39.67 ± 2.99	44.83 ± 3.31	41.0 ± 3.09
Total erythrocyte count ($10^6/mm^3$)	6.44 ± 0.54	7.12 ± 0.50	6.76 ± 0.57
Total leucocyte count ($10^3/mm^3$)	13.28 ± 1.37	14.94 ± 1.61	13.88 ± 1.46
Neutrophil (%)	70.5 ± 3.47	73 ± 3.12	70.33 ± 3.78
Lymphocyte (%)	25 ± 3.54	22 ± 3.38	25.33 ± 3.06
Eosinophil (%)	4.17 ± 0.60	5 ± 0.82	5 ± 0.86

Figures


Y
10
9
8
7
6
5
4
3
2
1
0
X axis - 1 cm = 0 1
Y axis - 2cm = 1
ED50 01738 mg/kg
Response
0·6
0 8
1 0
1 2
1 4
1 6
1 8
2 0
X
Log Dose


Y
X axis 2 cm = 0 1
Y axis - 2 cm = 1
ED50 31 62 mg/kg
Response
Log Dose
X
0
1
2
3
4
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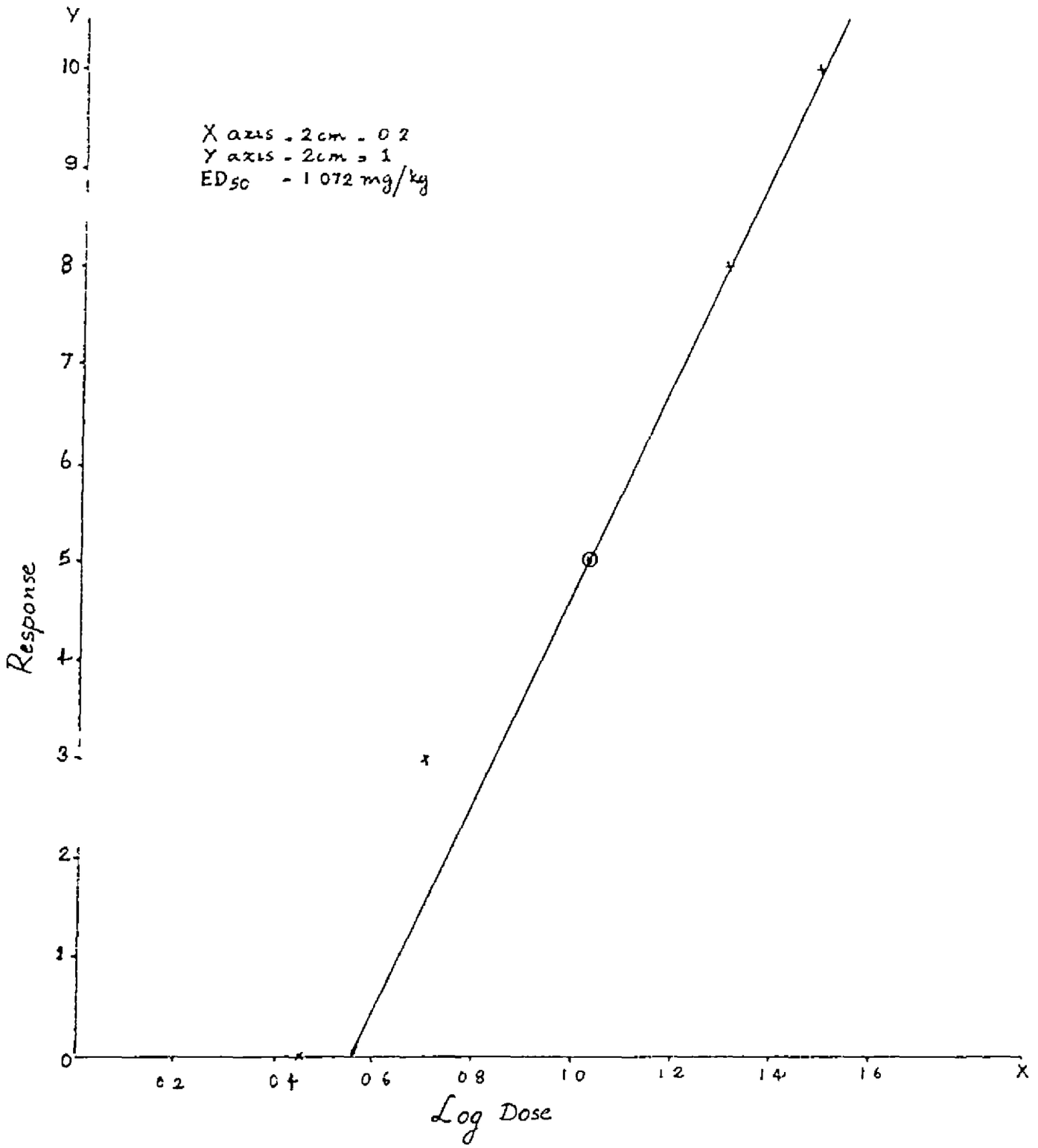
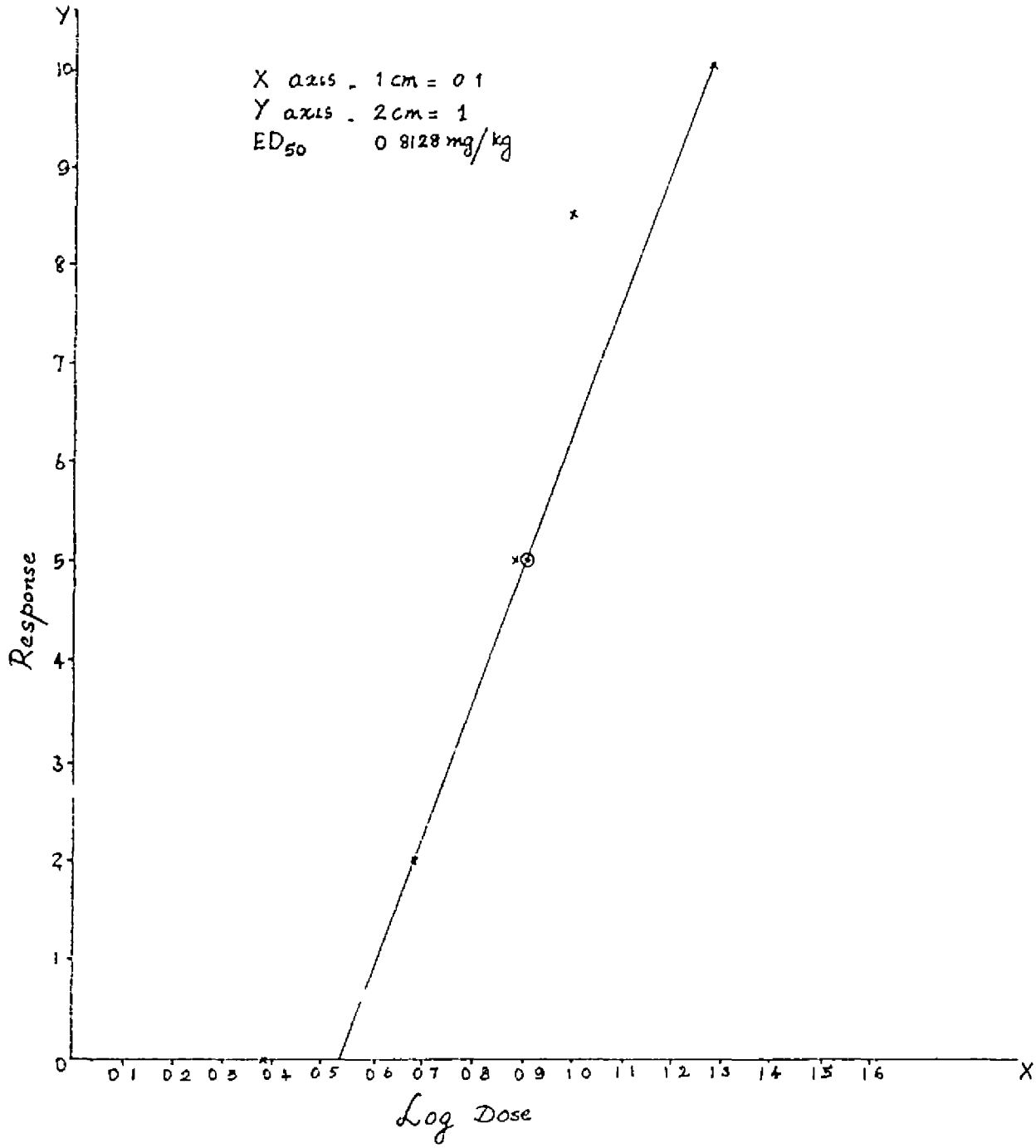
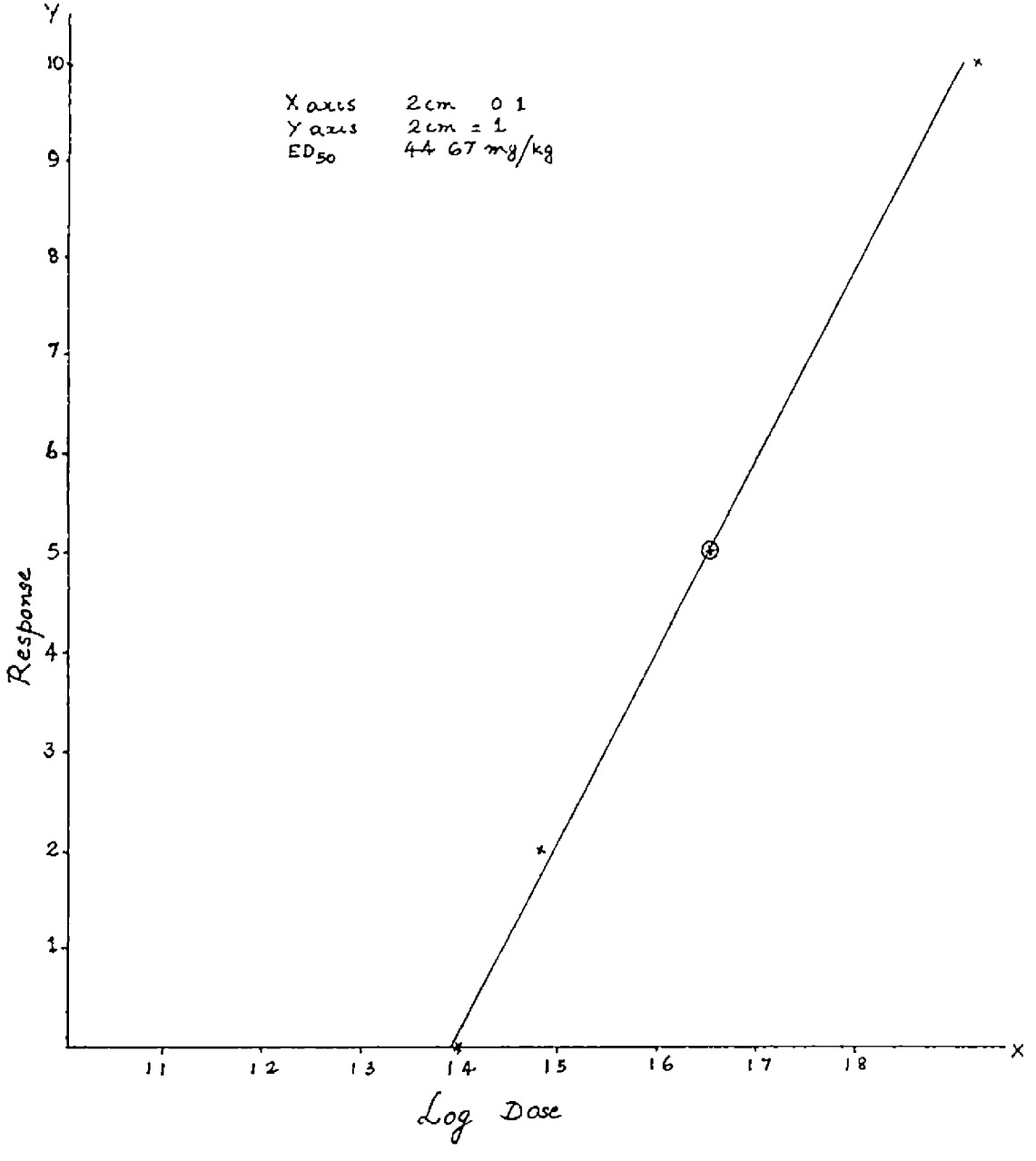
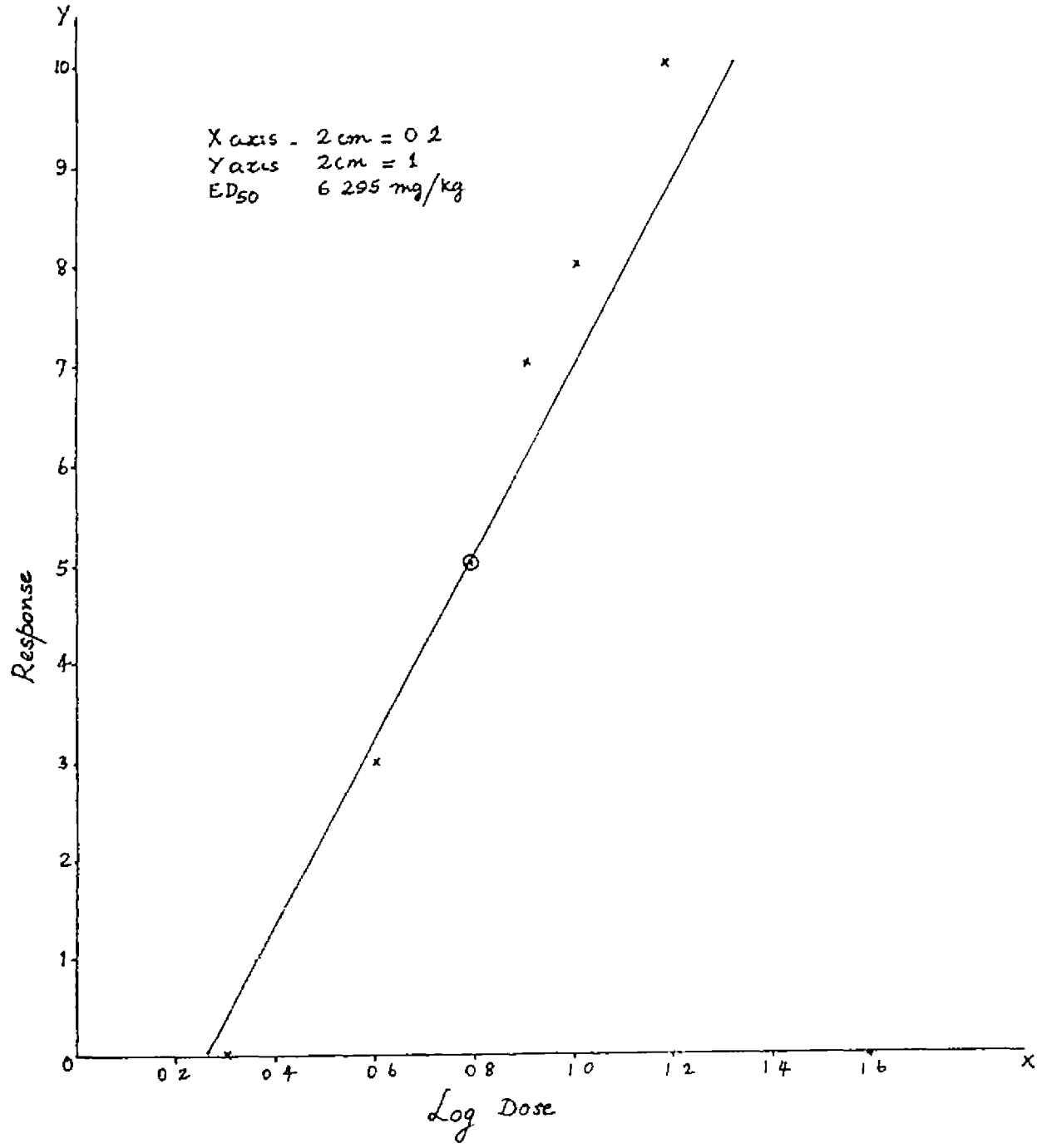
9
10
11
12
13
14
15
16
17
18


Y
10
9
8
7
6
5
4
3
2
1
0
X axis - 2cm - 0 2
Y axis - 2cm = 1
ED50 - 1 072 mg/kg
Response
0 2
0 4
0 6
0 8
1 0
1 2
1 4
1 6
X
Log Dose


X axis . 1 cm = 0 1
Y axis . 2 cm = 1
ED50 0 8128 mg/kg
Response
Log Dose
Y
X
0
1
2
3
4
5
6
7
8
9
10
0 1 0 2 0 3 0 4 0 5 0 6 0 7 0 8 0 9 1 0 1 1 1 2 1 3 1 4 1 5 1 6


Y
10
9
8
7
6
5
4
3
2
1
X axis 2cm 0 1
Y axis 2cm = 1
ED50 44 67 mg/kg
Response
11
12
13
14
15
16
17
18
X
Log Dose


Y
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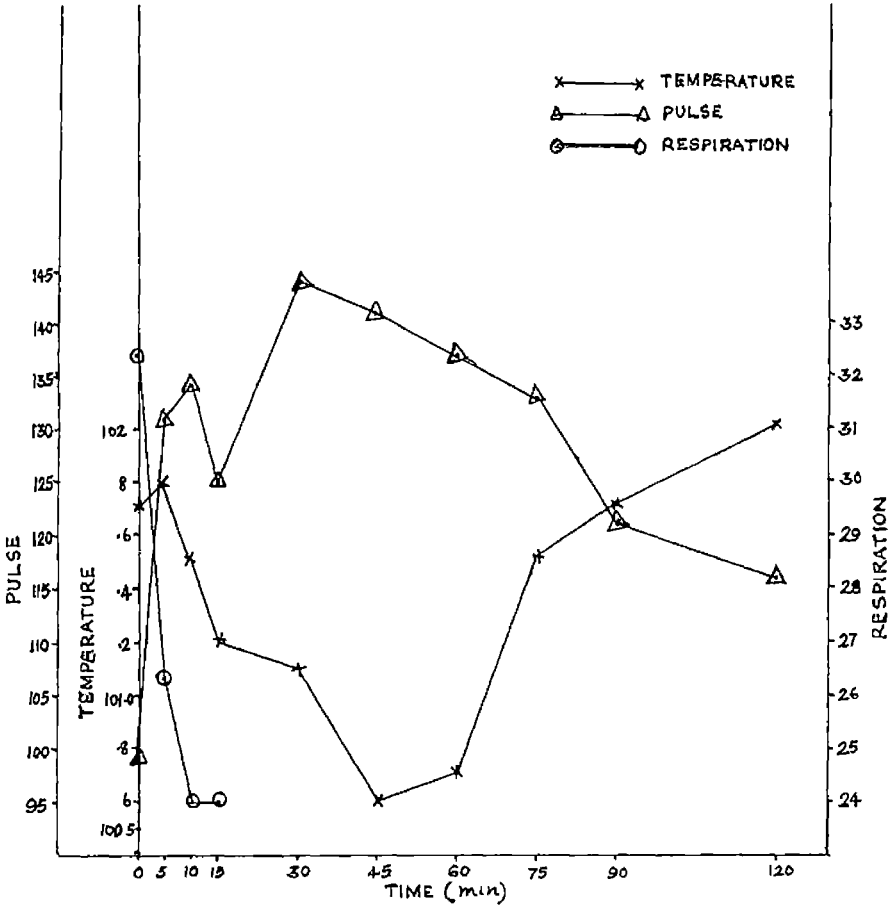
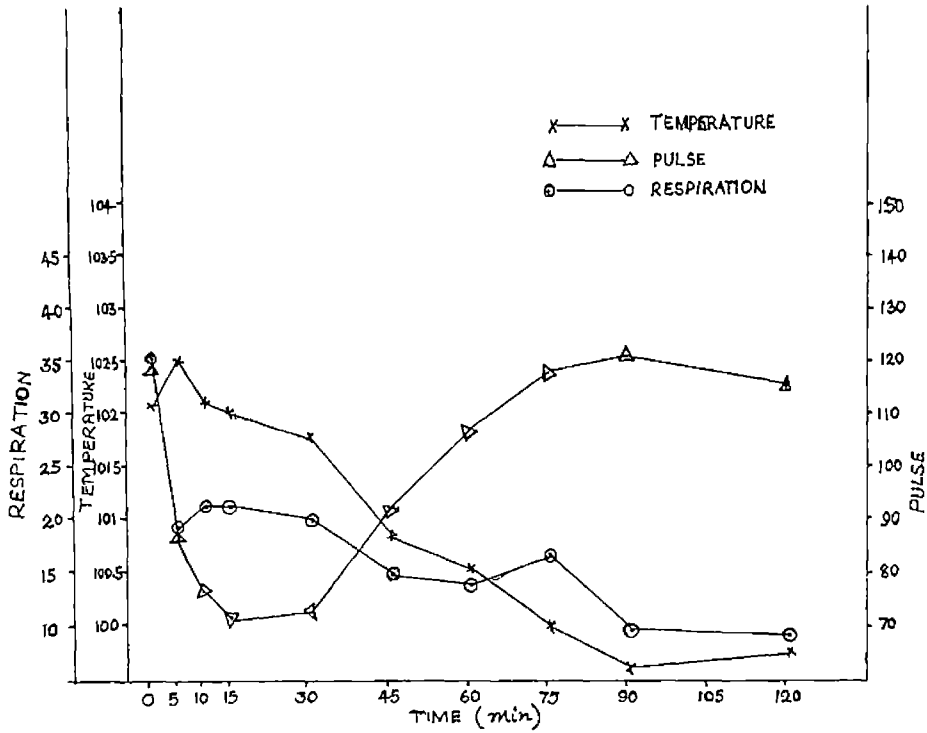
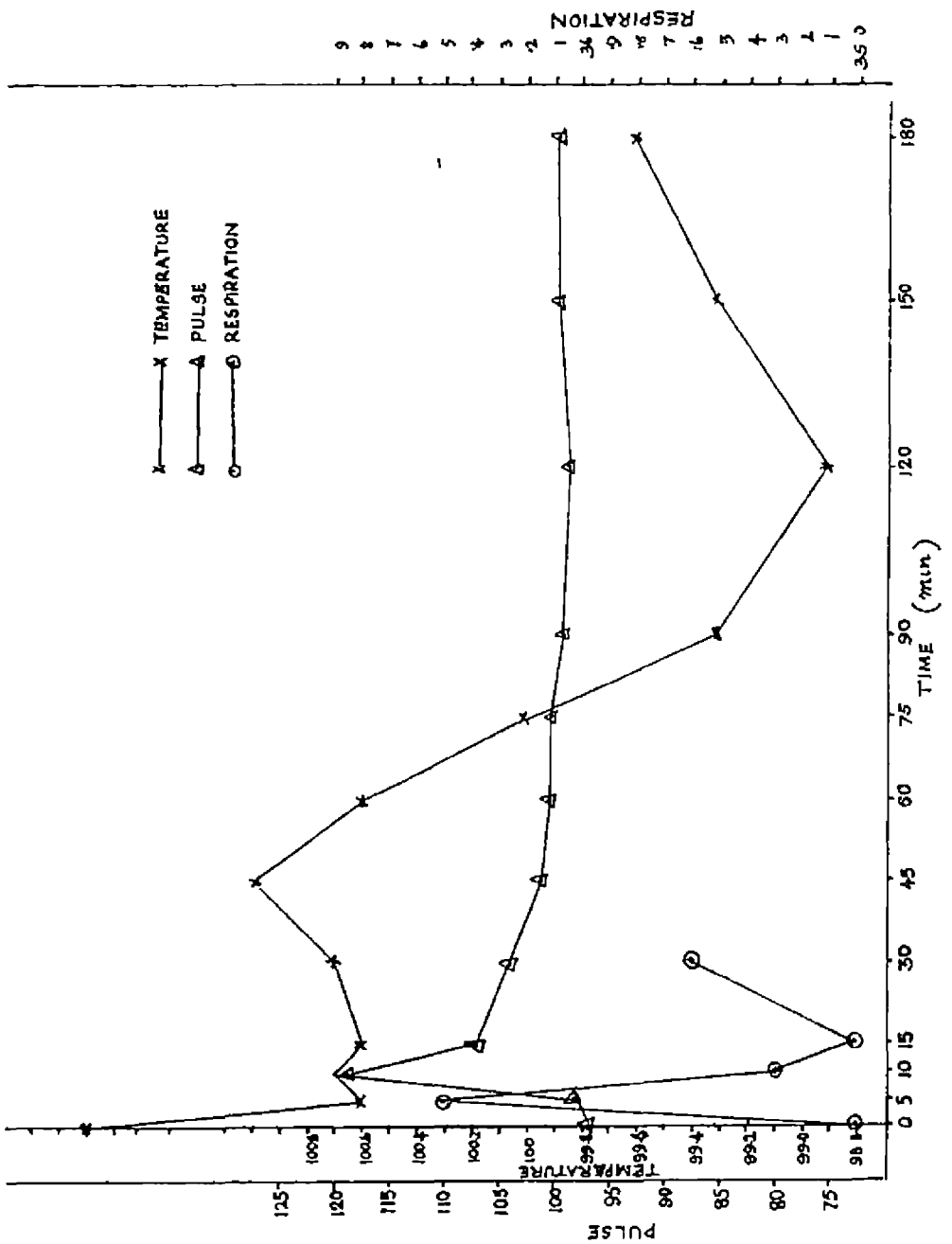
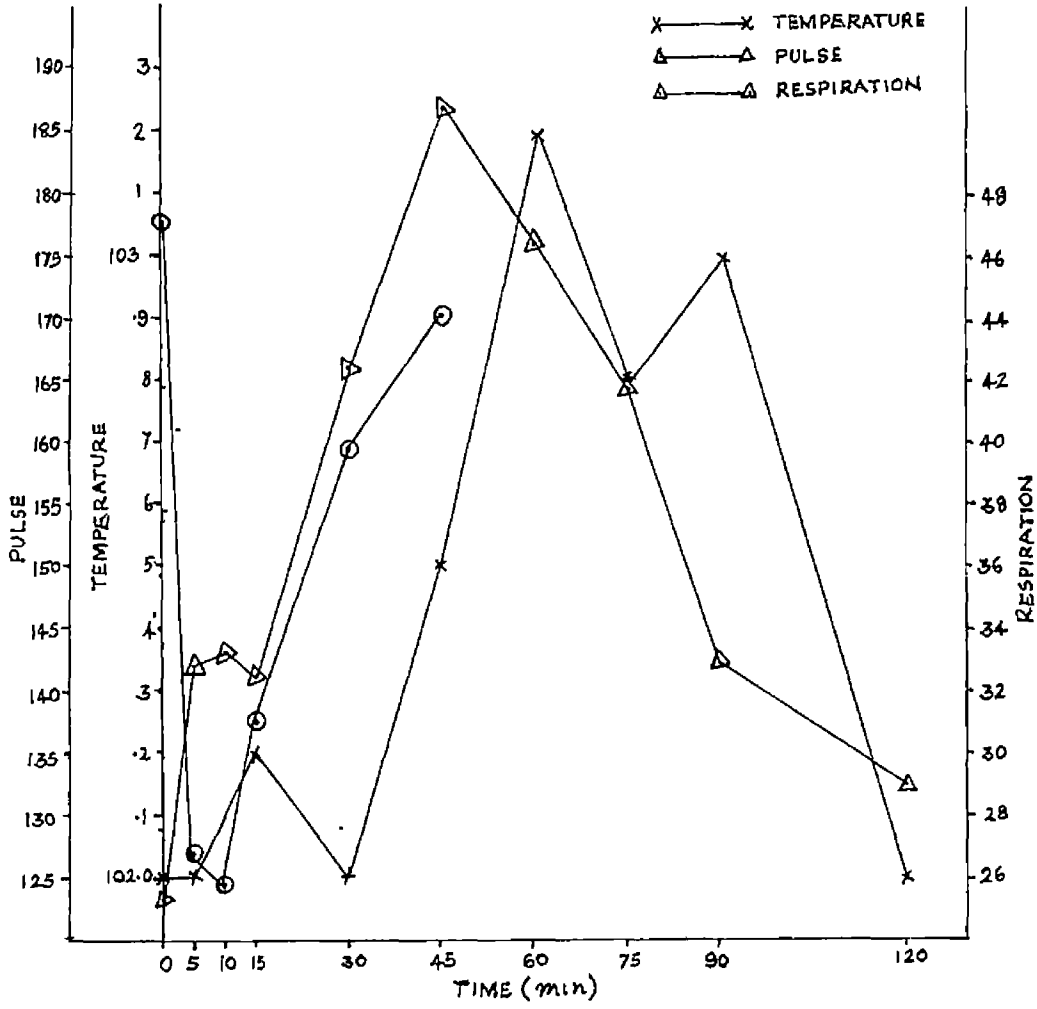
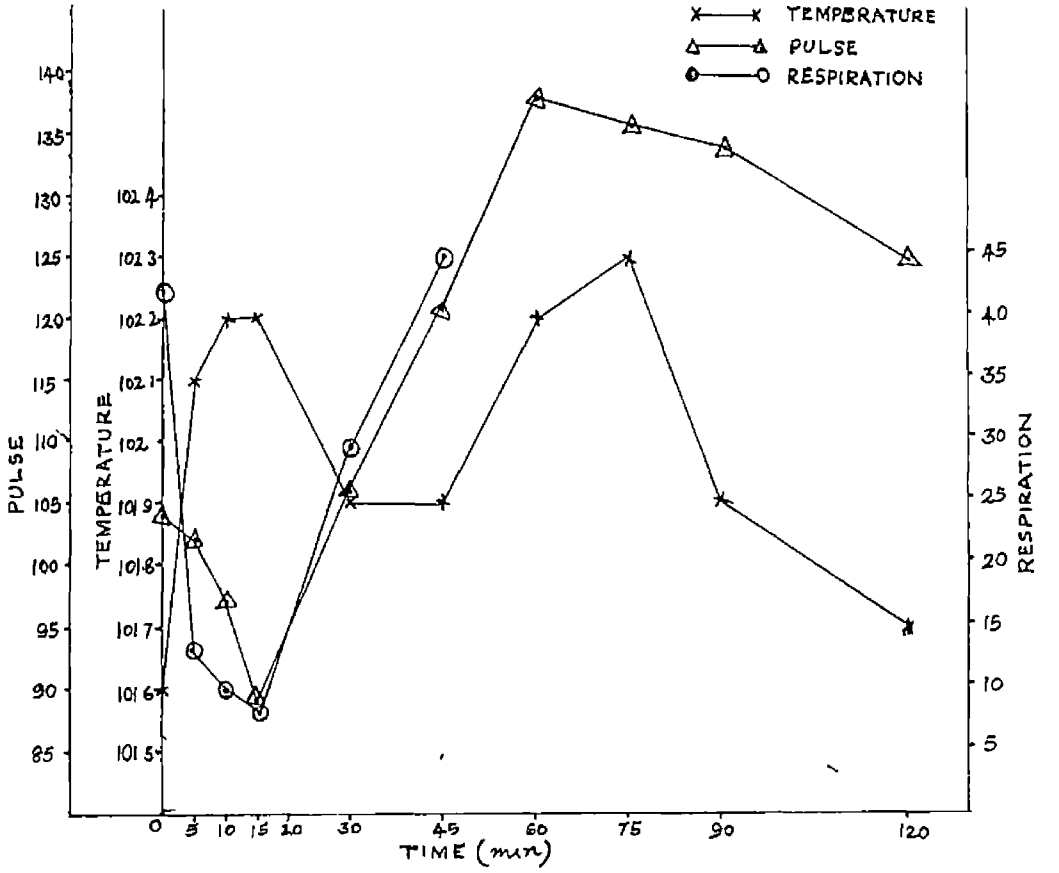
9
8
7
6
5
4
3
2
1
0
X axis - 2 cm = 0 2
Y axis 2cm = 1
ED50 6 295 mg/kg
Response
0 2
0 4
0 6
0 8
1 0
1 2
1 4
1 6
X
Log Dose


TEMPERATURE
PULSE
RESPIRATION
PULSE
TEMPERATURE
RESPIRATION
TIME (min)
145
140
135
130
125
120
115
110
105
100
95
102
8
6
4
2
101.0
8
6
100.5
33
32
31
30
29
28
27
26
25
24
0
5
10
15
30
45
60
75
90
120


TEMPERATURE
PULSE
RESPIRATION
RESPIRATION
TEMPERATURE
PULSE
TIME (min)
0 5 10 15 30 45 60 75 90 105 120
104
103.5
103
102.5
102
101.5
101
100.5
100
45
40
35
30
25
20
15
10
150
140
130
120
110
100
90
80
70


TEMPERATURE
PULSE
RESPIRATION
TIME (min.)
0 5 10 15 30 45 60 75 90 120 150 180
125 120 115 110 105 100 95 90 85 80 75
1008 1004 1000 996 992 988
TEMPERATURE
PULSE
RESPIRATION
TEMPERATURE
PULSE
RESPIRATION


TEMPERATURE
PULSE
RESPIRATION
PULSE
TEMPERATURE
RESPIRATION
TIME (min)
0 5 10 15 30 45 60 75 90 120
190 185 180 175 170 165 160 155 150 145 140 135 130 125
3 2 1 103 ·9 8 7 6 5 4 ·3 ·2 ·1 102·0
48 46 44 42 40 38 36 34 32 30 28 26


TEMPERATURE
PULSE
RESPIRATION
PULSE
TEMPERATURE
RESPIRATION
TIME (min)
140
135
130
125
120
115
110
105
100
95
90
85
102.4
102.3
102.2
102.1
102
101.9
101.8
101.7
101.6
101.5
45
40
35
30
25
20
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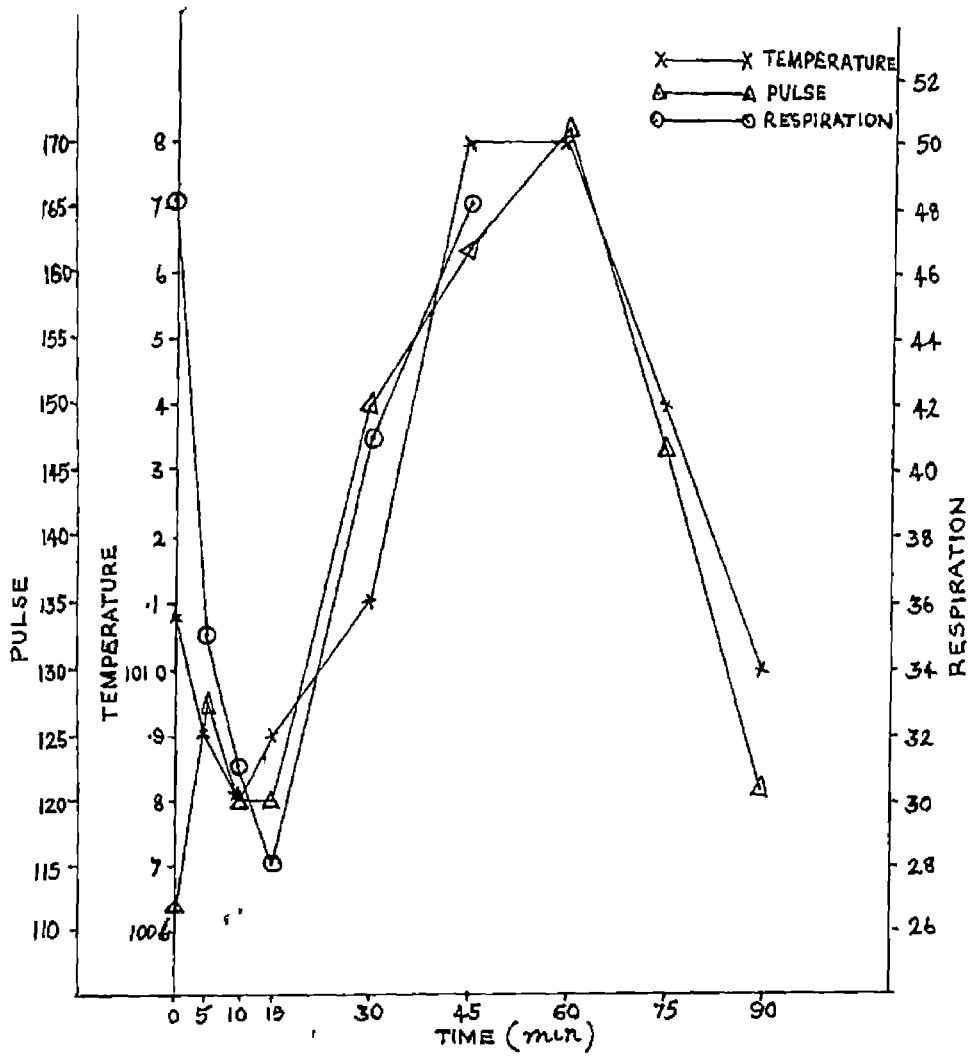
10
5
0
5
10
15
20
30
45
60
75
90
120


TEMPERATURE
PULSE
RESPIRATION
PULSE
TEMPERATURE
RESPIRATION
TIME (min)
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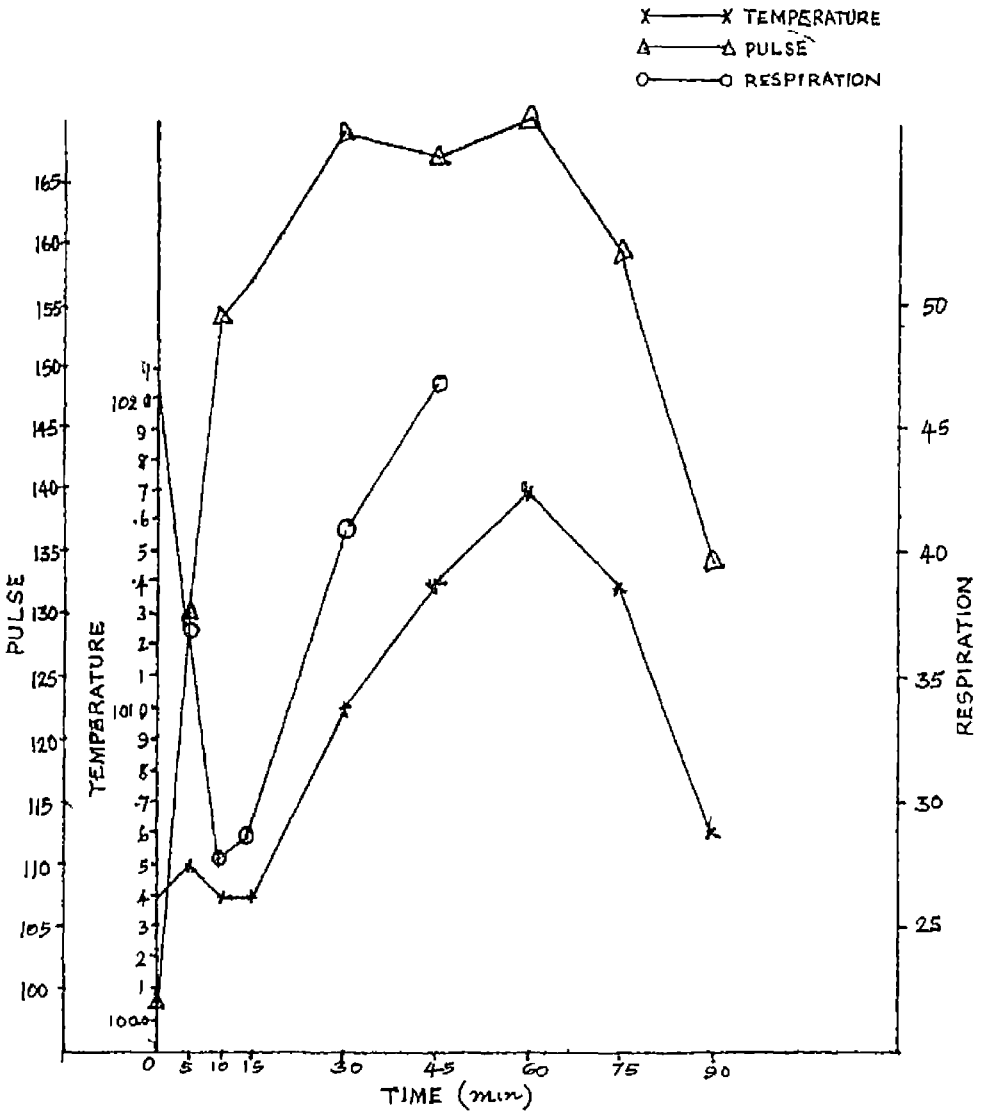
170 165 160 155 150 145 140 135 130 125 120 115 110
8 7 6 5 4 3 2 1 101 0 9 8 7 1006
52 50 48 46 44 42 40 38 36 34 32 30 28 26


TEMPERATURE
PULSE
RESPIRATION
PULSE
TEMPERATURE
RESPIRATION
TIME (min)
0
5
10
15
30
45
60
75
90

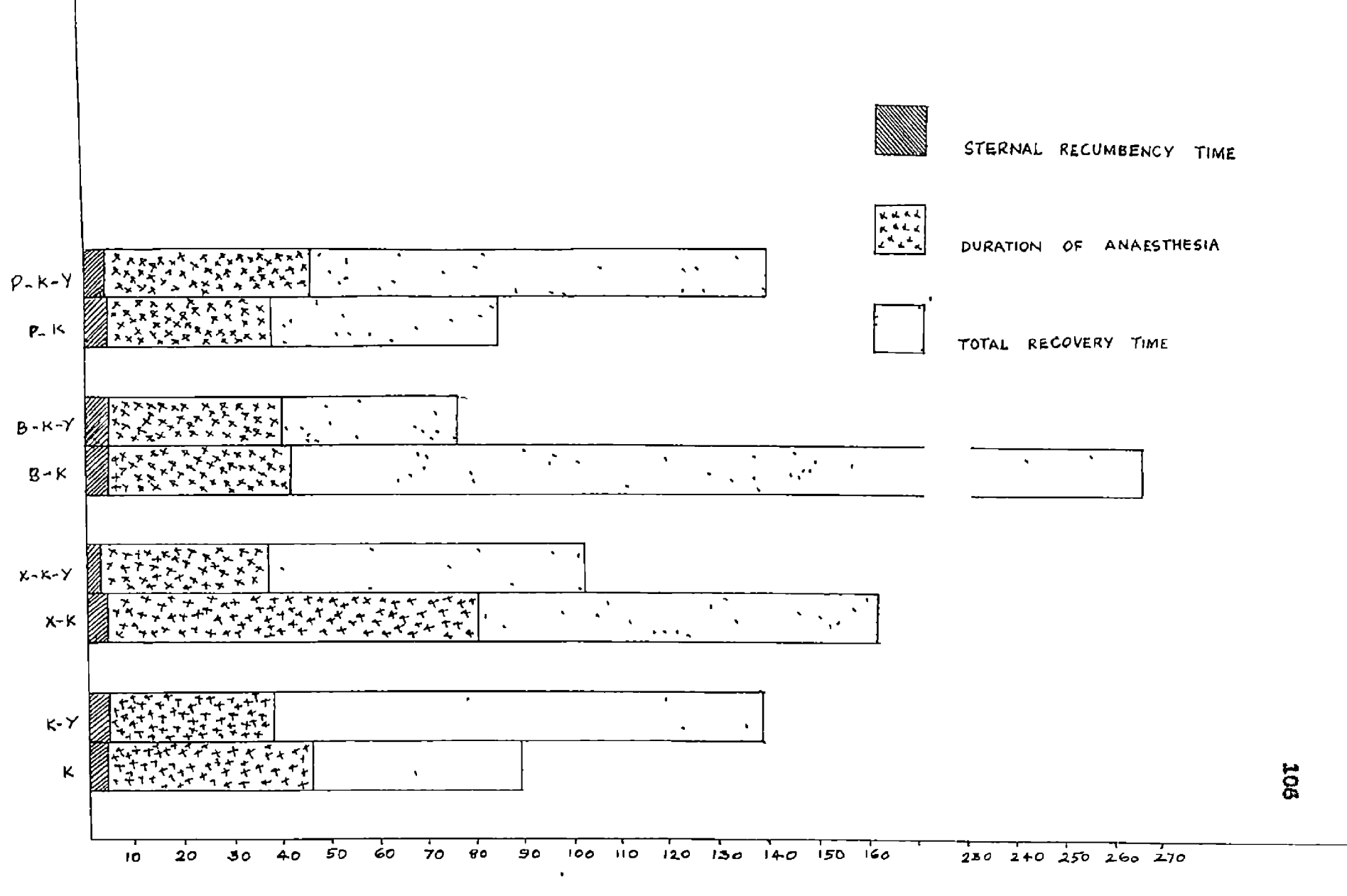
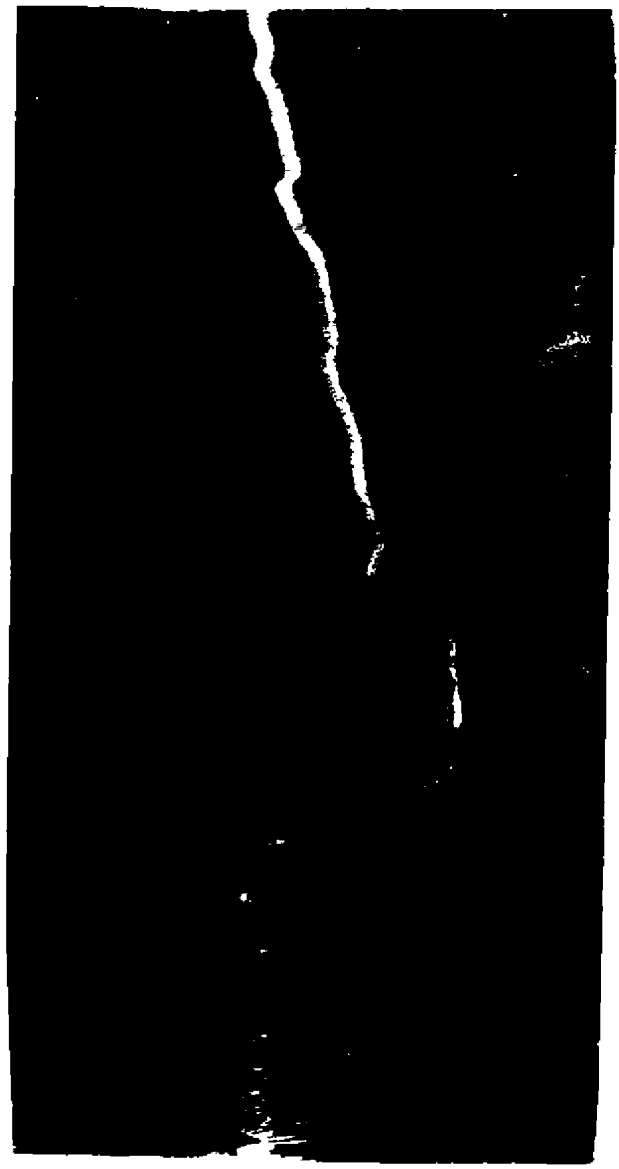

STERNAL RECUMBENCY TIME
DURATION OF ANAESTHESIA
TOTAL RECOVERY TIME
P-K-Y
P-K
B-K-Y
B-K
X-K-Y
X-K
K-Y
K
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
230
240
250
260
270

Fig. 16. Kymographic recording of the effect of yohimbine on blood pressure after xylazine-ketamine anaesthesia in dogs



CHAPTER V

Discussion

DISCUSSION

In the first part of the experiment the ED_{50} values for the three drugs, buprenorphine, pentazocine and xylazine were assessed using analgesiometer in rats and tail clip method in mice.

V.1.A. Buprenorphine.

The present study revealed that the ED_{50} of buprenorphine in rats and mice was 0.25 ± 0.094 mg/kg and 0.9827 ± 0.0751 mg/kg (intraperitoneally) respectively. This result is not in agreement with the result obtained by Cowan et al. (1977b) in which the ED_{50} in rat (tail flick method) was 1.6 mg/kg intraperitoneally and in mice (tail flick) was 2.4 mg/kg intraperitoneally. This difference can be attributed to variations in the method adopted for the study or to difference, in the intensity of heat source used.

The duration of analgesia exhibited by rats and mice in the present study was approximately 6 and 5 h respectively. Cowan et al. (1977b) found that the duration of analgesia was approximately 8 h. This difference might be attributed to the method adopted in each study.

V.1.B. Pentazocine.

The ED_{50} of pentazocine by rat tail pressure test was 8.8 mg/kg intraperitoneally (Cowan et al., 1977b) while by mouse and rat tail flick method it was greater than 30 mg/kg (Cowan et al., 1977b). In the present study the ED_{50} by rat

tail flick method was 32.60 ± 0.071 mg/kg and mouse tail clip method was 48.50 ± 0.323 mg/kg.

V.1.C. Xylazine.

The present study revealed that the ED_{50} of xylazine in rats and mice intraperitoneally was 1.424 ± 0.229 mg/kg and 7.523 ± 0.047 mg/kg respectively. Kanniappan (1974) reported that the ED_{50} of xylazine in rat was 2.08 ± 0.37 mg/kg and in mice 9.90 ± 2.08 mg/kg subcutaneously. This difference in ED_{50} might be due to difference in the route of administration like intraperitoneal and subcutaneous. Intraperitoneal administration facilitates; easy absorption of the drug, hence low dosages will be sufficient.

In the second part of the experiment, the effect of buprenorphine, pentazocine and xylazine on ketamine anaesthesia was studied.

V.2.A. Since the maximum and minimum body weights of animals in each group did not have much variation, it did not effect the experimental results.

V.2.B. The volume of the drugs were calculated based on the body weight of the animals.

V.2.C.a. Sternal recumbency time.

Average sternal recumbency time was minimum in the group B (X-K), then group A (K), group C(B-K) and group D(P-K) respectively. This indicated that premedication with xylazine reduced the induction time. In the present study the induction

time was 4.17 min. George et al. (1987) reported an induction time of 4 min. after xylazine-ketamine administration in a bonnet monkey. George et al. (1987) also reported sternal recumbency time of 2 min. after xylazine administration in a captive lion.

V.2.C.b. Clinical signs.

There was shivering and rigidity of the head and neck region and cataleptic immobility in group A(K). Similar observations were reported by Hoeppner and Short (1971) in cats, Deyoung et al. (1972) and Haskins et al. (1985) in dogs. In ketamine, catalepsy could be due to muscarinic-nicotinic cholinergic imbalance. The ketamine induced muscle rigidity might be due to stimulation of central adrenergic receptors (Deyoung et al., 1972). Haskins et al. (1985) recommended that dogs should be given adjunctive sedative or tranquillizer premedication, when ketamine alone is to be used.

There was profuse salivation, the eyelids were open and fixed stare. Parsania et al. (1977) also reported similar observations in dogs. The salivation might be attributed to cholinergic stimulation by ketamine.

The administration of xylazine, resulted vomiting in 3 to 5 min. in all animals. Lacuata and Leon (1973) reported a vomiting time of 1.5 to 1.8 min in cats after intravenous administration of xylazine. This difference in vomiting time might be due to the difference in the route of administration. Since intravenous administration resulted in rapid action of

the drug, reduction in vomiting time could be expected. Colby et al. (1984) demonstrated emetic action of xylazine in cats. He proved that xylazine acts on chemoreceptor trigger zone and this action might be mediated by an opiate type of receptor.

Xylazine pre-medication resulted in loss of pedal reflex. This indicated that xylazine-ketamine anaesthesia provides a satisfactory surgical anaesthesia with excellent analgesia. All the animals in group C (B-K) showed marked salivation in 3 to 10 min. after administration of the drugs. This might be attributed to the action of buprenorphine on opioid receptors. In this group, unlike in the group A, the tremors and convulsions were absent. This could be due to the CNS sedation produced by buprenorphine. Prolonged sleeping for 3 to 5 h duration can be attributed to the hypnotic effect of buprenorphine.

In group D(P-K) profuse salivation was observed after 10 to 15 min of pentazocine administration. Similar observation was reported by Davis and Sturm (1970), Cooper and Organ (1977) and Miner and Lossaco (1984). The salivation could be due to its action on opioid receptors. The convulsions, muscle rigidity and staring look might be the effect of ketamine which was explained earlier. All the animals in this group produced whining noise during recovery. The delirium and dreams during recovery from anaesthesia caused this reaction. It could be also due to the action of pentazocine on

opioid receptors which modified the behavioural pattern. The licking movements might be attributed to its action on opioid receptors. Dodman et al. (1988) reported that the licking was caused by the release of opioids and subsequent action on opioid receptors.

A significant reduction in rectal temperature was noticed in all the groups. Hypothermia in cats during ketamine anaesthesia was reported by Hoeppner and Short (1971). Fall in rectal temperature during xylazine-ketamine anaesthesia was reported by Karl et al. (1974) in cats, Kumar et al. (1976) in goats and Kumar and Singh (1979) in calves. This depressant effect on rectal temperature might be attributed to general sedation, CNS depression, reduced metabolic rate and inhibition of skeletal muscle movements. Pandey and Sharma (1986) reported significant fall in body temperature in dogs injected with diazepam and pentazocine. The present study also reported similar results.

A significant increase in pulse rate was noticed in group A(K) while a significant decrease observed in group B(X-K). The groups C(B-K) and D(P-K) showed a transient increase followed by a decrease. Haskins et al. (1983) observed an increase in pulse rate during ketamine anaesthesia. This could be due to centrally mediated generalised increase in sympathetic tone. The decreased vagal tone and interference with norepinephrine uptake by the sympathetic nerve endings might have also contributed to the increased pulse rate. Haskins et al. (1986)

reported reduction in heart rate in xylazine-ketamine anaesthesia. This decrease in pulse rate was a characteristic response to xylazine administration. This might be caused by a direct or indirect increase in vagal tone or decrease in sympathetic activity. Kumar et al. (1979) and Peshin et al. (1980) suggested that the bradycardia after xylazine administration might be due to cardiac depression or peripheral vasodilation as a result of central vagal effect.

The transient increase in pulse rate in group C(B-K) might be attributed to the increase in sympathetic tone by ketamine and further decrease could be due to sedation and cardiovascular depression contributed by buprenorphine. Cowan et al. (1977a) reported decrease in heart rate in dogs and rats after buprenorphine administration.

The transient elevation of pulse rate in group D(P-K) might be contributed by a rise in catecholamine concentration in the plasma by pentazocine and an increase in sympathetic tone by ketamine. But the decrease in pulse rate might be due to sedation and parasympathetic stimulation by pentazocine.

There was significant reduction in respiration rate in group A(K), B(X-K) and C(B-K). But there was no variations noticed in group D(P-K). The reduction in respiration rate might be due to reduction in oxygen consumption by the brain. Hollwahn et al. (1970) suggested that it might be the effect of direct inhibitory action of xylazine on medullary centre. Haskins et al. (1965) observed similar observations after

xylazine-ketamine anaesthesia. Cowan et al. (1977a) reported reduction in respiration rate after buprenorphine administration in rats and mice. The depression of respiration rate after buprenorphine and pentazocine could be due to its action on opioid receptors. Taylor et al. (1984) reported that there was no variations in respiration rate after pentazocine administration. This is in agreement with the results obtained in the present study.

V.2.C.c. Duration of anaesthesia.

The duration of anaesthesia was maximum in the group B (X-K) and minimum in the group D(P-K). Amend et al. (1972) reported that premedication with xylazine prolonged the duration of anaesthesia. This could be due to the sedation analgesia and muscle relaxation produced by xylazine, resulting from the stimulation of $\alpha 2$ receptors and subsequent inhibition of norepinephrine release.

V.2.C.d. Regaining of sternal recumbency time.

The time for regaining of sternal recumbency was maximum in group B(X-K). The other groups did not show much variation. This indicated that only xylazine was able to potentiate the ketamine anaesthesia.

V.2.C.e. Mean standing time.

The standing time was also prolonged in group B(X-K). This could be due to the sedation and muscle relaxation produced by xylazine. There were no significant variations in other groups observed.

V.2.C.f. Total recovery time.

The mean total recovery time was maximum in group C(B-K), then group B(X-K), A(K) and D(P-K) respectively in the order of decreasing duration. The prolonged total recovery time in group C(B-K) might be attributed to the buprenorphine induced sleeping which lasted for about 5 to 6 h.

V.2.C.g. Haemogram.

The significant reduction in haemoglobin, packed cell volume and total erythrocyte count in group A(K) and B(X-K) indicated that the xylazine and ketamine will induce temporary anaemia. Kumar et al. (1974) suggested that the temporary anaemia was resulted from the pooling of erythrocytes in the spleen. Taylor et al. (1984) reported that minor changes in blood cell counts might be related to stress and splenic engorgement associated with ketamine anaesthesia. The buprenorphine-ketamine combination showed no effects on haematocrit, but pentazocine-ketamine showed slight elevation. This might be due to increased permeability of vascular tissue and escape of fluid into extravascular space or due to release of catecholamine by pentazocine, which resulted in splenic contraction and increased haematocrit value.

A slight reduction in leucocyte count in group A(K) and D(X-K) was attributed to adrenocortical stimulation and subsequent effect of glucocorticoids on circulating neutrophils and lymphocytes.

There was no significant variation in neutrophil, lymphocyte and eosinophil count in group A(K), B(X-K) and C(B-K). But there was significant neutropenia with lymphocytosis observed in group D(P-K). The neutropenia might be attributed to the stress and adrenocortical stimulation after pentazocine administration.

In the third part of the experiment, reversal of anaesthesia using yohimbine was studied.

V.3.A. The maximum and minimum body weights of the animals in each group did not have much variations from the mean. So they got only little effect in the experiment.

V.3.B. The drugs were injected to the groups, E, F, G and H in the same order as described earlier and yohimbine was injected 15 min. later. None of the animals showed any untoward effects during injection of the drugs.

V.3.C.a. Sternal recumbency time.

Average sternal recumbency times were same as in the second part of the experiment, since same medicaments were given for induction of anaesthesia.

V.3.C.b. Clinical signs.

Salivation was noticed in all animals in all the groups. This might be due to cholinergic stimulation by yohimbine. Convulsive movements were noticed in group E(K-Y). Ramsay <u>et al</u>. (1983) also made similar observations after yohimbine administration. All the animals showed panting type of

respiration, excitement and hyperaesthesia during recovery. The panting type of respiration might be due to reversal of respiratory depression. Rapid respiration rate during recovery in yohimbine administered dogs was reported by Hatch et al. (1982). Similar observations were also reported by Cronin et al. (1983). Hatch and Ruch (1974) reported excitement and hyperaesthesia after yohimbine administration. This might be due to reversal of anaesthesia by yohimbine. Antagonism of ketamine may occur from release of central neuronal dopamine and norepinephrine (Booth and McDonald, 1982). Yohimbine and 5-HT activate the autonomic nervous system and cause anxiety like state.

The reversal of rectal temperature was noticed in all the groups. This could be due to the stimulant effect of yohimbine and subsequent elevation of metabolic rate.

Yohimbine reversed the xylazine and ketamine induced bradycardia. Pulse rate was significantly increased in all the groups. The bradycardic effect of xylazine has been attributed to decreased sympathetic outflow from the CNS and increased vagal tone due to facilitation of baroflex and decreased release of norepinephrine from the sympathetic nerve endings. All these effects are mediated by alpha 2 adrenergic receptors and are antagonized by yohimbine (Hsu and Lu, 1984). Hsu and Lu (1984) reported that yohimbine increases heart by promoting sympathetic outflow from CNS and inhibiting baroceptor action. Renecker and Olsen (1985) also reported increase in heart rate after yohimbine in deer.

Hsu et al. (1989) reported significant increase in respiration rates in dogs after yohimbine administration. In the present study also, all the groups showed an increase in respiration rate after yohimbine administration. Yohimbine has been shown to antagonize xylazine induced respiratory depression in cats (Hsu, 1993) and in mule deer (Jessup et al., 1983). Jessup et al. (1985) observed an increased respiration rate and depth after yohimbine administration.

V.3.C.c. Duration of anaesthesia.

Duration of anaesthesia was significantly reduced in group F(X-K-Y). This could be due to reversal of xylazine-ketamine anaesthesia by yohimbine. Xylazine sedation and analgesia are ascribed to stimulation of central presynaptic adrenoceptors. This prevents the norepinephrine release, by inhibiting the calcium influx which preceeds the release of norepinephrine. Since yohimbine is an alpha 2 antagonist all the above actions of xylazine can be prevented (Hsu, 1991). Further yohimbine might have a stimulant effect which shortens ketamine induced anaesthesia (Hatch et al., 1983). In the present study the duration of anaesthesia was slightly reduced in group E(K-Y) and G(P-K-Y), but slightly increased in group H(P-K-Y). This increased duration of anaesthesia in group D(P-K-Y) indicates the failure of yohimbine to reverse this combination. The reason for this was not clearly understood.

V.3.C.d. Regaining of sternal recumbency time.

Regaining of sternal recumbency time was significantly

reduced in group F(X-K-Y). This indicates an early arousal from the anaesthesia and hence effective reversal of xylazine-ketamine anaesthesia by yohimbine. Some of the effect of ketamine can also be reversed. But the effects of buprenorphine and pentazocine cannot be reversed by yohimbine.

V.3.C.e. Mean standing time.

There was considerable decrease in standing time in group F(X-K-Y). This also indicated an effective reversal of xylazine-ketamine anaesthesia by yohimbine. Both yohimbine and xylazine compete at α 2 receptors (Goldberg and David, 1983). The prolonged standing time in group E(K-Y) and H(P-K-Y) might be due to hypotension. The effect of yohimbine on blood pressure was studied with the help of kymograph. The observation suggested a fall in blood pressure after yohimbine administered intravenously. The kymograph recording is shown in Fig.16. Goldberg and David (1983) also reported lowered blood pressure in anaesthetised dogs after yohimbine. Buprenorphine induced sedation and sleepiness might be overcome by the stimulant effect of yohimbine. This explains the slight decrease in standing time in group G(P-K-Y).

V.3.C.f. Total recovery time.

The total recovery time was significantly decreased in group F(X-K-Y) and G(P-K-Y). This indicated an effective reversal in these two groups. Yohimbine was reported to prevent and reverse the CNS depression (Hatch et al., 1982)

in dogs (Kitzman et al., 1982) in cattle and (Jessup et al., 1983) in mule deer. The present study reported a prolonged recovery time in group E(K-Y) and H(P-K-Y). Similar observations were reported by Kitzman et al. (1984) in horses after administration of 4-aminopyridine and yohimbine. This might be due to the fall in blood pressure after yohimbine, as explained earlier.

V.E.C.G. Electrogram.

The changes in haematocrit observed in the second part of the experiment were reversed by yohimbine administration. The total leucocyte count showed a slight increase in all the groups. This might be due to the stimulant effect of yohimbine, which produced excitement and epinephrine release and hence leucocytosis. The differential leucocyte count did not show much variations.

CHAPTER VI

Summary

SUMMARY

The experiments were conducted in three different parts.

In the first part of the experiment, the ED_{50} of the three drugs namely buprenorphine, pentazocine and xylazine were determined using the analgesiometer (tail flick method) in rats and tail clip method in mice.

Six different dosages (0.03075, 0.0675, 0.125, 0.25, 0.5 and 0.75 mg/kg) were administered in rats intraperitoneally and analgesia was tested using analgesiometer. The ED_{50} of buprenorphine in rats was found to be 0.25 ± 0.084 mg/kg. The ED_{50} of buprenorphine in mice (tail flick method) was found to be 0.9827 ± 0.751 mg/kg intraperitoneally. The doses administered were 0.25, 0.5, 0.75, 1 and 1.5 mg/kg. The ED_{50} of pentazocine in rats by tail flick method was 32.60 ± 0.071 mg/kg. The doses administered were 15, 20, 25, 30, 35 and 40 mg/kg intraperitoneally. The ED_{50} of pentazocine in mice by tail clip method was found to be 40.50 ± 0.323 mg/kg by administration of six different doses (20, 30, 40, 45, 50 and 60 mg/kg) intraperitoneally in mice. The ED_{50} of xylazine for analgesia was 1.424 ± 0.229 mg/kg in rats (tail flick method). The different doses administered were 0.25, 0.5, 1, 2 and 3 mg/kg intraperitoneally. The ED_{50} of xylazine in mice (tail clip method) was found to be 7.523 ± 0.47 mg/kg. The different doses administered were 2, 4, 6, 8, 10 and 12 mg/kg intraperitoneally.

In the second part of the experiment the influence of

buprenorphine, pentazocine and xylazine analgesia on ketamine anaesthesia was studied in dogs. Twenty-four animals were divided into four groups (A, B, C and D) containing six animals each. Volume of drug administered were calculated according to their body weights and all the drugs were injected intramuscularly. The drugs were administered in the following sequence.

Group A - Ketamine (20 mg/kg) -(K)

Group B - Xylazine (2 mg/kg) + ketamine (15 mg/kg) - (X-K)

Group C - Buprenorphine (0.03 mg/kg) + Ketamine (15 mg/kg) -(B-K)

Group D - Pentazocine (2 mg/kg) + Ketamine (15 mg/kg) -(P-K)

The sternal recumbency time, clinical signs, duration of anaesthesia, regaining of sternal recumbency time, mean standing time, total recovery time and haemogram were studied.

The sternal recumbency time was 4.33 $\pm$ 1.20 min. in group A(K), 4.16 $\pm$ 1.20 min. in group B(X-K), 4.67 $\pm$ 0.67 min. in group C(B-K) and 4.67 $\pm$ 1.28 min. in group D(P-K).

Untoward reaction like salivation were present in group A(K), C(B-K) and D(P-K). Rigidity was present in group A(K) and D(P-K). Significant reduction in rectal temperature and respiration was observed in group A(K), while the pulse rate was significantly increased. There was significant reduction in temperature, pulse and respiration in group B(X-K). In group C(B-K) and D(P-K), there was significant reduction in rectal temperature. Pulse rate showed a

transient increase followed by a decrease in groups C(B-K) and D(P-K). No variation in respiration rates observed in early stages in group C(B-K) and D(P-K). Panting type of respiration was observed during recovery in groups A(K), C(B-K) and D(P-K).

Average duration of anaesthesia was 45.67 ± 3.67 min. in group A(K), 79.83 ± 2.45 min. in group D(X-K), 42 ± 4.39 min. in group C(B-K) and 29.5 ± 4.22 min. in group D(P-K). The xylazine-ketamine combination provides maximum duration of anaesthesia.

The regaining of sternal recumbency time during recovery was 50 ± 2.89 min., 83.83 ± 5.29 min., 46.67 ± 4.21 min. and 34.17 ± 3.52 min. in groups A, D, C and D respectively.

The average standing time was 72 ± 6.92 min., 106.17 ± 7 min., 68.33 ± 2.47 min. and 62.5 ± 3.82 min. in groups A(K), D(X-K), C(B-K) and D(P-K) respectively.

The total recovery time was 99.17 ± 17.58 min. in group A(K), 161.67 ± 11.00 min. in group B(X-K), 265.03 ± 24.10 min. in group C(B-K) and 84.17 ± 3.95 min. in group D(P-K).

All the above results indicated that only xylazine can potentiate the ketamine anaesthesia and xylazine-ketamine combination is better combination compared to buprenorphine-ketamine and pentazocine-ketamine. This xylazine-ketamine combination provide sufficient analgesia and muscle relaxation for prolonged surgical procedures.

The study of haemogram showed that the haemoglobin, packed cell volume and total erythrocyte counts decreased at 30 min. after drug administration in group A(K) and B(X-K), while there was no statistically significant variation in groups C(B-K) and D(P-K).

There was no significant variations in total leucocyte count and differential leucocyte count in groups A(K), B(X-K) and C(B-K) while the group D(P-K) showed a significant reduction in 30 min. after administration of the drug.

In the third part, the reversal of anaesthesia using the α_2 blocker yohimbine was studied. Twenty-four animals were divided into four groups (E, F, G and H) containing six animals each. The drugs were injected in the same order as in the second part of the experiment. Along with that yohimbine (0.25 mg/kg in groups E, G and H and 2 mg/kg in group F) was administered 15 min. later. The same parameters as in the second part of the experiment were studied.

The sternal recumbency time was same as in the previous experiment, since the same drugs were given for induction of anaesthesia.

Untoward effects exhibited by the animals after administration of yohimbine were salivation, panting and hyperaesthesia during recovery.

Rectal temperature, pulse and respiration increased in all the groups. This indicated reversal of anaesthesia by yohimbine.

The average duration of anaesthesia was 34.33 ± 1.65 min., 37 ± 2.33 min., 35.67 ± 4.57 min. and 35 ± 5.79 min. in groups E(K-Y), F(X-K-Y), G(B-K-Y) and H(P-K-Y) respectively. The duration of anaesthesia was significantly decreased in group F(X-K-Y).

The regaining of sternal recumbency time was 38.33 ± 1.67 min. in group E(K-Y), 39.17 ± 2.39 min. in group F(X-K-Y), 40.83 ± 4.72 min. in group G(B-K-Y) and 40.33 ± 5.14 min. in group H(P-K-Y).

The mean standing time was 109.17 ± 17.58 min. in group E(K-Y), 82.5 ± 12.09 min. in group F(X-K-Y), 58.33 ± 4.77 min. in group G(B-K-Y) and 80.33 ± 6.31 min. in group H(P-K-Y).

The mean total recovery time was 138.33 ± 18.33 min. in group E(K-Y), 102.5 ± 11.88 min. in group F(X-K-Y), 75.83 ± 7.12 min. in group G(B-K-Y) and 129.17 ± 5.54 min. in group H(P-K-Y).

From the study of the haemogram, it was observed that, the changes in haematocrit observed in the second part of the experiment was completely reversed.

By comparing the results of the third part of the experiment with the second part, it was obvious that yohimbine produced effective reversal of anaesthesia in xylazine-ketamine combination, but fail to reverse ketamine and ketamine-buprenorphine combination and produced prolongation of recumbency time in ketamine and ketamine-pentazocine combination.

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ABSTRACT

The experiments were conducted in three different parts. In the first part of the experiment the ED_{50} of the three drugs namely buprenorphine, pentazocine and xylazine was determined using the analgesiometer (tail flick method) in rats and tail clip method in mice. The ED_{50} of buprenorphine in rats and mice was 0.25 ± 0.084 mg/kg and 0.9827 ± 0.0751 mg/kg intraperitoneally. The ED_{50} of pentazocine in rats was 32.60 ± 0.071 mg/kg and in mice 48.50 ± 0.323 mg/kg. The ED_{50} of xylazine for analgesia in rats and mice was 1.424 ± 0.229 mg/kg and 7.523 ± 0.47 mg/kg respectively.

In the second part of the experiment the influence of buprenorphine, pentazocine and xylazine analgesia on ketamine anaesthesia in dogs were studied. Twenty-four animals divided into four groups (A(K), B(X-K), C(B-K) and D(P-K) were administered with ketamine (20 mg/kg), xylazine (2 mg/kg) plus ketamine (15 mg/kg), buprenorphine (0.03 mg/kg) plus ketamine (15 mg/kg) and pentazocine (2 mg/kg) plus ketamine (15 mg/kg) respectively. The sternal recumbency time, clinical signs, duration of anaesthesia, regaining of sternal recumbency time, mean standing time, total recovery time and haemogram were studied. The sternal recumbency time was minimum in xylazine administered group. Untoward reactions like salivation and rigidity of the muscles were observed in groups A(K) and D(P-K). There was significant reduction in rectal temperature in all

the groups. The pulse rate was elevated in group A(K) and depressed in group B(X-K), while a transient increase followed by decrease showed in group C(B-K) and D(P-K). Respiratory depression was observed in groups C(B-K) and D(P-K). Average duration of anaesthesia was maximum in group B(X-K) while all other groups showed almost similar durations of anaesthesia. The time for regaining of sternal recumbency was also maximum in group B(X-K), then the groups A(K), C(B-K) and D(P-K) respectively. Mean standing time was maximum in group B(X-K). The rest of the groups followed the same pattern as above. The total recovery time was maximum in group C(B-K), then group B(X-K), A(K) and D(P-K) respectively. The study of haemogram showed that, the haemoglobin, packed cell volume and erythrocyte counts decreased at 30 min. after drug administration in groups A(K) and B(X-K) while there was no significant variation in group C(B-K) and D(P-K). The group D(P-K) showed a significant reduction in leucocyte count, while there were no variations in other groups observed.

In the third part of the experiment the reversal of anaesthesia using the α_2 blocker yohimbine was studied. Twenty-four animals divided into four groups (E, F, G and H) were administered with the same drugs as in the second part of the experiment. Along with that yohimbine (0.25 mg/kg in group E, G and H and 2 mg/kg in group F) was administered 15 min. later. The groups E, F, G and H were designated as K-Y, X-K-Y, B-K-Y and P-K-Y respectively. Untoward effects

exhibited after yohimbine administration were salivation, panting and hyperaesthesia during recovery. Rectal temperature, pulse and respiration were increased in all the groups. The duration of anaesthesia, regaining of sternal recumbency time, mean standing time and total recovery time were significantly reduced in group F(K-K-Y), while there was no variations in the above parameters in group E(K-Y). Only the total recovery time significantly reduced in group G(B-K-Y) and prolongation of standing time and total recovery time was observed in group H(P-K-Y). The haematological changes noticed in the second part of the experiment were completely reversed by yohimbine.