STUDIES ON THE INFLUENCE OF CHLORAMPHENICOL ON THIOPENTONE SODIUM ANAESTHESIA IN DOGS

BY

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THESIS

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DECLARATION

I hereby declare that this thesis entitled "STUDIES ON THE INFLUENCE OF CHLORAMPHENICOL ON THIOPENTONE SODIUM 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 of any degree, diploma, associateship, fellowship or other similar title of any other University or Society.

21-12-78.

ARAVINDAKSHAN, C.M.

Mannuthy,

21-12-1978.

CERTIFICATE

Certified that this thesis entitled "STUDIES ON THE INFLUENCE OF CHLORAMPHENICOL ON THIOPENTONE SODIUM ANAESTHESIA IN DOGS" is a record of research work done independently by Sri. Aravindakshan, C.M. under my guidance and supervision and that it has not previously formed the basis for the award of any degree, diploma, fellowship or associateship to him.

Dr. Zacharias Cherian
Associate Professor
(Chairman, Advisory Committee).

Mannuthy,

21-12-1978.

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Aravindakshan, C.M.

DEDICATION

I dedicate this thesis to those poor souls which were sacrificed for this study.

Aravindakshan, C.M.

C O N T E N T S

INTRODUCTION

INTRODUCTION

The last half a century has been remarkable for the extraordinarily large number of drugs of all types which have been introduced into anaesthetic practice. In considering the history of development of anaesthesia, it can be observed that the discovery of new drugs and agents has not proceeded at a uniform rate. From 1840 to 1850 nitrous oxide, ether, chloroform and ethyl chloride were used, but it was over 80 years before any new general anaesthetic agents were added that were to have a permanent place in the practice of anaesthesia. During the years 1930 to 1935 a great increase in knowledge occurred with the introduction of hexobarbitone, thiopentone, cyclopropane and trichloroethylene, with the result that anaesthesia became firmly established as a medical speciality (Cole, 1969).

General anaesthesia is a state of unconsciousness produced by a process of controlled, reversible intoxication of the central nervous system, in which there is a lowered sensitivity to stimuli. Thus an anaesthetic agent may be defined as a substance which produces in a controllable manner both loss of consciousness and an absence of motor response to noxious stimuli (Hall, 1971).

Immediately after the publication of Morton's work

on the administration of ether to human beings (1846), it was adapted in animals by the Royal Veterinary College, London.

Intravenous anaesthesia by chloral hydrate in animals was first described by Humbert in 1875. Its action is chiefly one of the depression of cerebral cortex and when it is administered as a basal narcotic, there occurs little or no preliminary excitement before depression. It depresses myocardium and also causes a fall in blood pressure. In all animals chloral hydrate is slow in crossing the blood-brain barrier and hence it is difficult to assess the effects produced by the drug as the intravenous injection progresses and also the narcosis continues to deepen for several minutes even after the injection is terminated (Hall, 1971).

The introduction of barbiturates, about 30 years ago, brought a revolution in the field of general anaesthesia in dogs and cats. Pentobarbitone (Nembutal) was first used as a general anaesthetic in Veterinary Surgery in America by Kreutzer, Haigler and Sweeb in 1931. However, since its action is too prolonged for many purposes, other barbiturates were tried in veterinary anaesthesia. Among them, thiopenton sodium has emerged as the 'standard' intravenous anaesthetic with which all others are compared (Hall, 1971).

Though thiopentone sodium is used widely in veterinary medicine the duration of surgical anaesthesia produced by it is too short. Many operations in small animal practice requires a longer duration of anaesthesia than that is induced by a single injection of thiopentone. For this reason the injection of thiopentone sodium has to be repeated as and when required. Such repeated injections have been found to prolong the recovery time and increase the toxicity of the drug.

However, prolonged sedation involving deep narcosis is essential in dogs undergoing intensive therapy for major trauma resulting from fighting, accidents etc. This deep sedation may be needed for two or more days and its safety, encounters difficult problems (Hall, 1971).

Antibiotics are employed in a variety of medical and surgical conditions in animals. The presurgical use of antibiotics for prophylaxis of bacterial infections had been studied and debated in literature (Burke, 1961; Bernad and Cole, 1964; Campbell, 1965; and Feltis Jr. and Hamit, 1967).

It is a common practice to anaesthetise dogs for surgical procedures and such animals are usually prophylactically protected with antibiotics, especially in planned surgery. Hence it is considered worthwhile to find out the influence of antibiotics on the duration of anaesthesia

induced by thiopentone sodium, which is commonly used in minor surgical interference requiring relatively short duration of surgical anaesthesia.

In view of the above situations a study was conducted to find out whether the antibiotics like chloramphenicol, streptomycin and kanamycin have any influence on thiopentone sodium anaesthesia in dogs.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Anaesthetic agents as a group exert clear depressant action on the reticular formation and affect this region early or even at the lowest active dose. Responses to afferent stimuli are prevented or reduced, recovery time of neurons is prolonged and outflows particularly for arousal and sensory modulations are blocked (Killam, 1962).

Mayer et al. (1959) studied the mechanism of passage of drugs into the brain and cerebro spinal fluid. The substances enter the central nervous system by a process of simple diffusion. The most important determinants of the rates of entry of drugs are the dissociation constant and the lipid solubility of the unionized forms. There is no demonstrable barrier to the passage of drugs and foreign compounds, which are highly lipid soluble.

The apparent similarity of the effect of various anaesthetics may not be a reflection of identical modes of action of all anaesthetics, but rather a reflection of the varying stability of different synapses. The location and mode of action of anaesthetics on various aspects of the synapse may differ between the anaesthetics (Wall, 1967).

Somjen (1963) and Somjen and Gill (1963) studied the mechanism by which diethyl ether and thiopentone interrupt

the transmission of the monosynaptic reflex in the mammalian spinal cord by recording ventral root potentials and by microelectrode studies of motor neurons. On ventral root recorus the voltage at which the propagated spike appears to depart from the synaptic potential, was reversibly increased by the administration of the drugs. The rate of rise of the synaptic potential was reduced.

Richards (1972) reported that pentobarbitone probably reduced the output of transmitter from the presynaptic nerve terminals of the olfactory cortex and that this mechanism could be the basis of the depressent actions of the barbiturates.

Barbiturates

Barbituric acid (Malonyl urea) results from the condensation of malonic acid and urea. It was synthesised in 1864 by Adolph von Baeyer and in the same year by Kekule in Ghent.

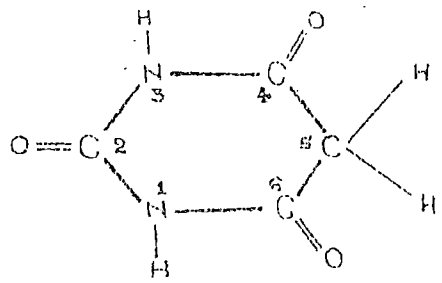
Urea + malonic acid ——————→ Barbituric acid.

Barbiturates are available as oxybarbiturates and thiobarbiturates. Barbiturates in which the oxygen at C_2 is replaced by sulphur are called thiobarbiturates. Thiobarbiturates are more lipid soluble than oxybarbiturates,

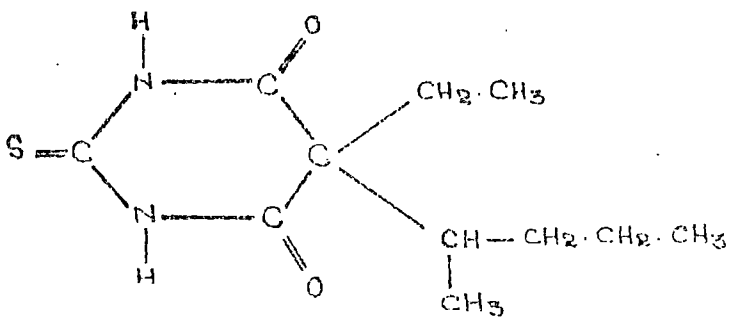
because of the electronegetivity of sulphur is nearly that of carbon, therefore the C = S group is nearly nonpolar. The thiobarbiturates have a very rapid onset and duration of central nervous system action and are more potent than the corresponding oxybarbiturates. Numerous thiobarbiturates have been synthesised, but only those with relatively high molecular weight have a satisfactory margin of safety for clinical use. The thiobarbiturates are employed almost solely as anaesthetic for intravenous or rectal administration. Thiopentone, the thio analog of pentobarbitone is taken as the prototype of the thiobarbiturates (Harvey, 1975).

King et al. (1957) suggested that the central nervous system depressant effect of barbiturates are due to functional block of ascending influences of the brain stem reticular formation. In greater concentration barbiturates exert a depressant influence directly upon thalamic relay nuclei.

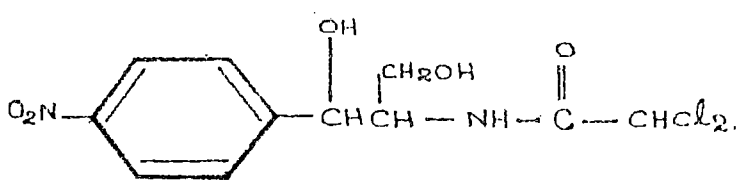
Barbiturates produces some local anaesthetic effect and according to Krupp et al. (1969) barbiturates block the action potential by increasing the surface pressure of the lipid layer of the excitable membrane and do not interfere with the calcium binding sites, which governs the increased membrane conductance during excitation.



BARBITURATE MOLECULE



THIOPENTONE



CHLORAMPHENICOL

Thiopentone sodium.

Thiopentone sodium is a yellow unstable, water soluble salt, marketed in ampoules of 0.5 g and 1 g. It is dissolved in water before administration and the solution should not be kept long, as hydrolysis occurs rapidly. No solution should be used after three days at room temperature (Brander and Pugh, 1971).

Administration of large doses of thiopentone in normal subjects caused significant and nearly proportional reduction in cerebral metabolite and cerebral blood flow and the cerebral vascular resistance was increased (Pierce et al. 1962). Hyperventilation during the anaesthesia produced no further reduction in oxygen consumption, although it decreased blood flow to extremely low levels.

Thiopentone has been shown to reduce cerebral oxygen consumption rate in man and experimental animals (Altenburg et al. 1969). The results confirmed a parallelism between functional and metabolic aspects of acute central nervous system tolerance to thiopentone.

Lesions in the septal area of the forebrain or in the dorsomedial tegmentum of the brainstem produced a prolongation of thiopentone induced sleep (Roth and Harvey,1968)

Early reports on the use of thiopentone suggested that

it was rapidly broken down in the body, hence the term 'ultra short acting', by which it became known. Further studies in animals showed that thiopentone had a marked cumulative action, the repeated administration of the same dose resulting in a gradual prolongation of narcosis with each successive injection. To explain the cumulative action of thiopentone and the prolonged narcosis which follows large total doses is that, normal organs are incapable of destroying more than a certain amount of the drug. It is also suggested that thiopentone caused liver dysfunction, the initial dose thereby reduced the ability of this organ to deal with supplementary doses (Dundee and Wyant, 1974).

Subjects who were administered thiopentone showed a loss of memory for events discussed while they were under sedation (Osborn et al. 1967). The authors tested the subjects for recognition memory of pictures and recall of associated pairs of letters, words and found out that the subsequent memory loss was correlated with the concentration of thiopentone in the venous blood.

Metabolism.

The three most important drug factors affecting the distribution and fate of barbiturates are:-

1. Lipid solubility (Partition coefficient)

2. Protein binding

3. Degree of ionization

Immediately after injection a large proportion of the barbiturate is rendered pharmacologically inactive by being bound to the non-diffusible constituents of the plasma. Thiobarbiturates are bound to a greater extent than their oxygen analogues, the figure for thiopentone being 65 to 75 per cent. The degree of binding varies with the pH, maximum at pH 8.0. With increasing barbiturate concentration, the percentage of the bound drug diminishes although the total amount inactivated by this means increased. At low concentrations practically all the drug is bound to the plasma protein especially to the albumin (Dundee and Wyant, 1974).

Thiopentone concentration in red cells is about 40 per cent of that found in the plasma (Dundee and Wyant,1974).

Short and Tumbleson (1973) reported that the binding of radio carbon labelled pentobarbitone and thiopentone increased during the first week of life.

The onset of hypnotic action following intravenous pentobarbitone is slower than comparable doses of thiopentone. This effect can be explained by the differences in partition coefficient of the two drugs. Thiopentone is largely nonionic at plasma pH and has a very high partition

coefficient, while pentobarbitone is even less ionised at pH 7.4 and is much less protein bound but, because of the low partition coefficient of the nonionised form, its penetration is very slow (Dundee and Wyant, 1974).

Mark et al. (1958) suggested that thiopentone passes into the brain more rapidly than do their oxygen analogue and this is probably due to their higher lipid solubility.

According to Brodie and Hogben (1957) thiopentone which has a high partition ratio between oil and water penetrated the central nervous system of dogs so rapidly that after intravenous injection, it appeared in maximal concentration in brain within one minute. Its passage into brain is so rapid that it must be unhindered by the blood brain barrier and the rate is presumably limited only by the rate of cerebral blood flow. Similarly the decline in plasma concentration of this barbiturate is mirrored closely by decline in the cerebro spinal fluid and brain levels. The rapid establishment of diffusion equilibrium between blood and brain has important clinical application as it is essential to the precise control of the depth of anaesthesia.

Drugs which quickly penetrate into brain will also diffuse out rapidly and soon be distributed to skeletal muscle and other tissues. Thus the onset of action of

thiopentone will be quicker than that of pentobarbitone and duration of its hypnotic effect will be correspondingly less (Dundee and Wyant, 1974).

Dundee and Wyant (1974) suggested that the immediate uptake of thiopentone by the brain is accompanied by a similar rapid uptake in other important non nervous tissues such as the liver and kidneys and the plasma levels falls quickly. The concentration of drug reaching the brain is thus lowered and as the brain content falls, anaesthesia lightens. It has also been shown that the cerebro spinal fluid concentration reaches a level almost as high as that of the unbound drug in the plasma and thereafter it declines as in other tissues.

Saidman and Eger (1966) on the other hand found an appreciable amount was metabolised in the dogs liver and this played an important role in the early rapid reduction of arterial thiopentone levels. It is believed that tissues other than the liver are quantitatively unimportant in the rapid detoxification of thiopentone in dogs (Meyers and Donpeoples, 1954).

Cooper and Brodie (1957) reported that in addition to liver, thiopentone is metabolised to a lesser extent in other tissues especially kidney and brain. The oxidation of pentobarbitone and thiopentone seem to be carried out by different catalytic anzymes.

A decrease in hepatic circulation in dogs produced a significant delay in the detoxication of thiopentone sodium. In normal dogs the fall of plasma levels of thiopentone is accelerated by autoperfusion of the liver and this procedure is suggested in severe thiopentone sodium poisoning not, responding to the usual therapy (Rappaport et al. 1956).

Thiopentone, both metabolised and deposited in fat, has a short life span in the blood and the nonfatty tissues (Loomis, 1974). For example, thiopentone which has a brief anaesthetic action has a life span of 15 minutes or less in blood following conventional single dose in man. This is because that portion of the drug which is in the blood rapidly undergoes conversion to non anaesthetic forms and the remainder of the drug is deposited in fat. Then, rapidly the drug diffuses from the fat to the blood and it is converted to inactive forms, so that the blood remains practically free of effective concentration of the drug.

With the exception of muscle and fat, the maximum tissue concentration of thiopentone is reached within one minute after a single intravenous injection. It is the rapid redistribution which is responsible for the short action of small doses. Despite the affinity of thiopentone to fat, uptake of the drug in adipose tissues is relatively

slow because of the poor blood supply and maximum deposition occurs only after 1½ to 2½ hours. By this time the concentration in the fat greatly exceeds that of other tissues (Dundee and Wyant, 1974).

Richards and Taylor (1956) noticed the presence of barbiturates practically in all tissues after its administration. During the period when the blood concentration is dropping rapidly the tissues may build up a concentration higher than the blood. After a time depending on barbiturate and dose, the blood and the tissues reaches the equilibrium. It is the rapid removal from the blood by the tissues, that is responsible for the short action of the so called 'ultra short acting barbiturates'.

Body fat and thiopentone.

Body fat plays a definite role in the duration of thiobarbiturates anaesthesia by extracting the drug out of the blood stream and then causing the blood concentration to fall below the level needed to maintain unconsciousness. However, the rate at which thiopentone moves into the fat from plasma is relatively slow as compared with the speed at which other tissues of the body take it out of the blood stream. The tissue affinity is more important for small doses of thiopentone causing short sleeping time, but with large or repeated doses, the fat plays an increasingly

important role in terminating anaesthesia (Richards and Taylor, 1956 and Goldstein and Aronow, 1960).

Potentiating Agents

A number of substances and drugs will potentiate and prolong the depressant effects of barbiturates especially the short acting ones. The important among them are the sedatives and hypnotics, narcotics, tranquilizers, inhalation anaesthetics, antihistamines and alcohol. The additive or potentiating effects of these compounds are understandable in as much as they all have depressant properties. The mechanism of action, other compounds which themselves do not produce central nervous system depression is more obscure. These compounds can exert an effect through alterations in pH or protein binding, which will modify the relationship between the diffusable and non diffusable component (Soma, 1971).

Winters et al. (1962) and Soma (1971) found that the feeding of high amounts of corn oil in rats reduced the thiopentone sleeping time by 30 per cent. The initial assumption of the mode of action is the trapping of the barbiturates in the chylomicrones within the blood stream. The thiobarbiturates enters the intestine and is trapped by the unabsorbed corn oil. Heparin will reverse the corn oil effect. Heparin does play a role in the plasma clearance of

chylomicrones and lipoproteins. This involves the disruption of neural fat into unesterified fatty acids, which will compete for binding sites on albumin making it less available for thiopentone.

In clinical practice Csoger and Kerek (1970) have shown that 0.1 mg/kg of 40 per cent sulphafurazole solution significantly reduced the dose of thiopentone required to induce sleep and anaesthesia in dogs by interfering with the binding of thiopentone to albumin.

Richards and Taylor (1956) reported the prolongation of barbiturate sleeping time in experimental animals by calcium, strontium, iodides, glycerine, glucose and sorbitol, phenyl boric acid and nitrites. The latter two, possibly due to vasodilating action. Various vasoactive drugs including kallikrein, acetyl choline, adenylic acid, vasopressin and epinephrine affected the duration of thiopentone and hexobarbitone anaesthesia in a manner which could not be attributed to their vascular effects.

Reserpine produces prolongation of barbiturate and ethyl alcohol sleep without any evident effect upon their metabolism. The administration of the lysergic acid diethyl amide (LSD) resulted in a marked reduction of the potentiating action of reserpine, while LSD alone did not modify barbiturate effect. The central effects of reserpine such

as the prolongation of barbiturate action, may be due to the release of serotonin (Richards and Taylor, 1956).

Peterson et al. (1950) found that treatment of dogs with para-amino acetophenone, an agent capable of producing methemoglobenemia resulted in the prolongation of thiopentone sodium anaesthesia by developing anoxia in dogs.

Pretreatment of rats with the antihistaminic drug, chlorcyclizine increased the activity of enzyme system in the liver microsomes that metabolize hexobarbitone, pentobarbiton and zoxazolamine (Conney and Burns, 1962).

It has also been reported by various authors that thiopentone sodium anaesthesia can be prolonged not only by the administration of sedatives and hypnotics, but also by a variety of drugs such as Glucose (Lamson et al. 1949), 2,4-dinitrophenols (Brody and Killam, 1952) and compounds which compete for protein binding (Lasser et al. 1963) and glucose and sodium lactate (Rajagopalan and Nayar, 1970).

Klide et al. (1974) reported that pretreatment with atropine significantly prolonged the thiopentone sleeping time in dogs. Similarly pretreatment of dogs with atropine and chlorpromazine resulted in an increase in the narcotic activity of thiopentone (Hatch, 1967).

Hatch (1972) studied the effect of autonomic blocking

agents in thiopentone anaesthesia and showed that propranolol reduced the dosage of thiopentone and duration of anaesthesia. But mecamylamine, trimethidinium, physostigmine, neostigmine and methysergide had no specific effects on plasma thiopentone concentration in dogs.

Heavner and Bowen (1968) observed reanaesthetisation of dogs, when they were given adrenergic substances like adrenaline and isoprenaline during the recovery time from thiopentone anaesthesia. The reanaesthetisation could not be correlated with alpha or beta adrenergic activity, the change in rate of thiopentone metabolism, central depressant action, redistribution of anaesthetic agent and/or increase in permeability of the blood-brain barrier.

Pentobarbitone inhibits catecholamine release by preventing a configurational change in the structure of the membrane of the chromaffin cells which is a necessary link between receptor activation and catecholamine release (Holmes and Schneider, 1973).

Duration of anaesthesia may be greatly affected by hormones and steroids when an ultra short acting barbiturate anaesthetic agent is administered. The predominant effect seen in this study was a shortening of anaesthetic response time which occurred with combination of progesterone,

testesterone, dexamethasone and prednisolone. Various steroid medications enhanced or diminished liver microsomal responses, thus affecting recovery from the anaesthesia.

Novick et al. (1966) reported that testesterone and methyl testesterone induced an increased hexabarbitone sleeping time and testesterone decreased the rate of hepatic microsomal metabolism of hexobarbitone in rats.

Rajagopalan and Marykutty (1973) found that administration of stilbesterol dipropionate, significantly enhanced the duration of surgical anaesthesia and sedation in dogs by thiopentone.

According to Vandam (1971) a number of other drugs can affect the response to anaesthetics or drugs used for anaesthesia. Several antibiotics, viz., neomycin, streptomycin and kanamycin can exert a competitive blocking action at the neuromuscular junction.

In the present study three antibiotics, viz., chloramphenicol, streptomycin and kanamycin were selected to study their influence, if any, on thiopentone sodium anaesthesia in dogs.

Chloramphenicol.

It is a broad spectrum antibiotic isolated from

Streptomyces venezulae, by Burkholder and his collaborators in 1948. It was synthesided in the following year and made available for clinical use.

Chloramphenicol is a white but sometimes slightly grey or yellow fine crystalline powder. It has a bitter taste and is only slightly soluble in water (1:400) but soluble in most of the organic solvents.

Aqueous solutions in distilled water can be kept for at least one month at normal room temperature without losing the potency. Solutions are relatively stable between pH 2.0 and pH 9.0, but strong alkaline solutions cause rapid decomposition. The powder and solutions are heat stable and solutions will withstand boiling for at least five hours.

Chloramphenicol is highly bacteriostatic and can be bactericidal. Peak plasma level of chloramphenicol is produced within one hour after parenteral routes and two hours after orally (Mercer et al. 1971; Pauli and English, 1971; Watson, 1974 and Shah et al. 1977).

Streptomycin.

Streptomycin is a narrow spectrum antibiotic obtained from Streptomyces griseus in 1943 by Schatz, Bugie and Waksman. It exerts its most potent effects on gram negative bacteria, on gram positive enterococci and on the acid fast

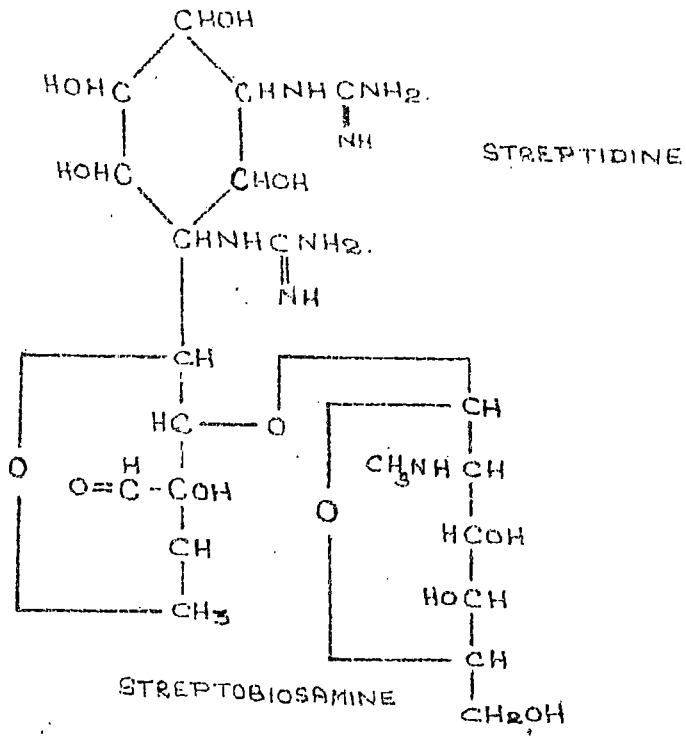
tubercle bacilli (Grollman and Grollman, 1970).

Many organic and inorganic salts have been prepared, of which the sulphate is the most important preparation since it causes least pain and irritation at the site of injection (Garrod et al. 1973).

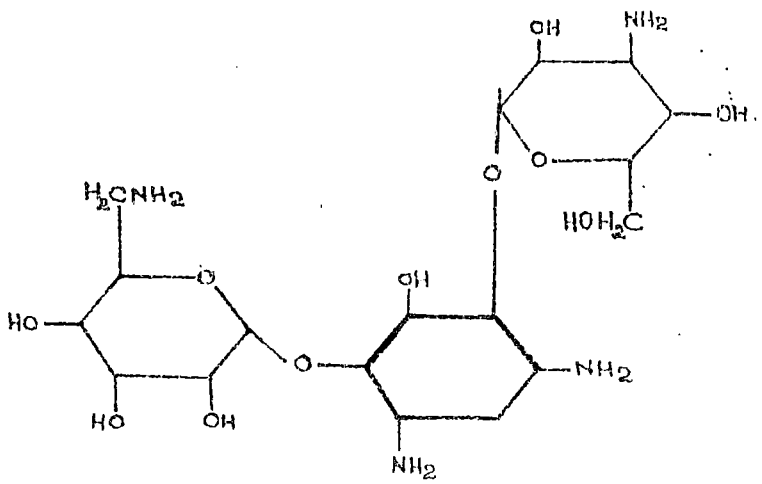
Streptomycin is a white crystalline substance with slight odour and saline taste. It is hygroscopic and highly soluble in water. Solutions darkens on exposure to light, but this darkening do not appreciably affect activity and solutions at pH 6.0 to 8.0 will retain potency for upto one month at room temperature. The potency is rapidly lost above 28°C. Any pH lower than pH 3.0 or higher than pH 8.0 hasten hydrolysis and irreversible destruction. The aqueous solutions buffered with sodium citrate will keep for at least one year without appreciable loss of potency (Brander and Pugh, 1971).

Kanamycin.

Kanamycin sulphate is a water soluble, broad spectrum antibiotic obtained from Streptomyces kanamyceticus, a straight chain aldohexamine consisting of two amino sugars glycosidically linked to deoxystreptamine. Kanamycin is bactericidal against a variety of gram positive and gram negative organisms and Mycobacterium tuberculosis (Grollman and Grollman, 1970).



STRETOMYCIN



KANAMYCIN

The drug is eliminated faster in dogs than other domestic animals. In this species a single intramuscular injection produces therapeutic blood levels for less than nine hours (Clark, 1977).

Andreini and Pignattelli (1972) reported that kanamycin is well absorbed after intramuscular injection in dogs and without undesirable side effects.

In man kanamycin is readily absorbed from parenteral routes and peak concentration occurs at approximately one hour after administration, following which there is a rapid decline of serum concentration over the subsequent 12 hours (Gronk and Naumann, 1959).

Adams (1975) studied the cardiovascular effects of aminoglycoside antibiotics (a group of antibiotics in which kanamycin and streptomycin are included) during pentobarbitone anaesthesia in dogs, cats and primate species. These antibiotics altered cardiovascular dynamics in anaesthetised animals and indicated that the deliterious effects may be related to modifications of calcium ion functions.

Aminoglycoside antibiotics, possess neuromuscular blocking effect during pentobarbitone anaesthesia and administration of neostigmine or calcium chloride reversed the antibiotic induced neuromuscular paralysis. Crawford and Bowen (1971) suggested that the function of calcium

antibiotic complex is involved in the neuromuscular blocking effect.

Adams and Russner (1972) reported that chloramphenicol do not possess neuromuscular blocking effect in cats which are anaesthetised with pentobarbitone.

Adams (1970) has been reported that chloramphenicol enhances markedly the anaesthetic activity of barbiturates like hexobarbitone, aminobarbitone and pentobarbitone. It has also been reported by Adams and Dixit (1970) and Ivascu and Isoc (1976).

Teske and Carter (1971) reported that chloramphenicol administered to dogs, orally, intramuscularly or intravenously prior to or concurrently with pentobarbitone resulted in prolonged anaesthesia.

MATERIALS AND METHODS

MATERIALS AND METHODS

A total number of 60 mongrel healthy, adult dogs of both sexes, weighing from 7.0 kg to 12.0 kg were selected for the trials. The experimental dogs (54 numbers) were divided into three groups (Group I, II and III) and each group was again divided into three batches, viz., A, B and C. The remaining six dogs were kept as control and were given only thiopentone sodium.

Drugs Used

1. Chloramphenicol.

Chloramphenicol (*VETYCETINE-TCF) was available in 30 ml multidose vials. Each ml of the preparation contains 100 mg of chloramphenicol I.P.

2. Streptomycin.

Streptomycin (**AMBYSTRIN-S - Sarabhai) was available as 0.5g, 0.75g and 1.0g vials. 0.5g vials were used for this study.

3. Kanamycin.

Kanamycin (@KANCIN - Alembic) was available as 0.5g and 1.0g vials. 0.5g vials were used for this study.

4. Thiopentone sodium.

Thiopentone sodium (@@INTRAVAL SODIUM - M&B) was available as 0.5g and 1.0g ampoules, with 10 ml and 20 ml of distilled water for injections. For the present study 0.5g ampoules were used.

Preparation of the Drugs

Since chloramphenicol (Vetycetine), available as water miscible solutions, it was used as such.

Streptomycin sulphate injectable solution was prepared by diluting each vial (0.5g) with 10 ml of distilled water (50 mg/ml).

Kanamycin sulphate solution was prepared by diluting 500 mg of the drug with 10 ml of distilled water (50 mg/ml).

Thiopentone sodium was used as a 2.5 per cent solution; 0.5g thiopentone sodium was diluted with 20 ml of distilled water (25 mg/ml).

Dosage and Administration

Chloramphenicol.

The dose of chloramphenicol used for the experimental study was 50 mg/kg body weight intramuscularly (Rajagopalan

et al. 1974). The same dose level was tried in this study.

Streptomycin.

A dose level of 10 mg/kg body weight intramuscularly was used.

Kanamycin.

The dose recommended by Hungerford (1970) was 10 mg/kg body weight intramuscularly. In the present study 10 mg of kanamycin sulphate per kg body weight was used.

Thiopentone sodium.

Rajagopalan et al. (1974) used thiopentone sodium at a dose level of 30 mg/kg body weight for their experiment study. The same dosage was adapted in the present study. It was administered intravenously as a 2.5 per cent solution

For the experimental dogs in batch A, under group I, chloramphenicol was given 30 minutes prior to the administration of thiopentone. Dogs in batch B under group I, received chloramphenicol one hour before thiopentone injection. Similarly dogs in batch C under group I were given chloramphenicol two hours prior to the administration of thiopentone.

The same procedure was adopted for the experimental dogs under group II and III, using streptomycin and

kanamycin respectively.

Blood samples were collected from all dogs before the administration of antibiotics and also after the recovery of consciousness. Blood samples were used for determination of packed cell volume (PCV) and erythrocyte sedimentation rate (ESR) values.

Procedure

The weight of the dogs were recorded prior to the administration of the drugs. Antibiotics were administered to the dogs as described above. The dogs were kept on the operation table on the lateral recumbancy and properly controlled. The cephalic vein or external saphenous vein was used for the intravenous administration of thiopentone sodiu

One third of the total calculated dose was injected fairly rapidly in order to bring the animal in sedation. Then the remaining solution was given slowly by watching the respiratory movements and reflexes, until the surgical plane of anaesthesia was achieved as evidenced by the abolition of pedal reflex. The duration of surgical anaesthesia was the time interval between the abolition of pedal reflex and its reappearance. Duration of the sleep was the interval from the time animal lost consciousness to the first conscious attempt of the animal to raise its head during recovery from the anaesthesia.

Control group.

Animals in the control group received only thiopentone sodium at a dose of 30 mg/kg body weight intravenously. The surgical anaesthesia and sleeping time were assessed as described in the experimental groups.

The blood samples (5 ml) were collected in clean vials which contained ethylenediaminetetraacetic acid (EDTA) as the anticoagulant (1 mg of EDTA/ml of blood). The packed cell volume (PCV) and erythrocyte sedimentation rate (ESR) of the samples were determined by the Wintrobe method, as described by Benjamin (1961).

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* Brand of chloramphenicol by M/s Rallis India Limited, Teddington Chemical Factory Division, Bombay-69.

** Brand of streptomycin sulphate by M/s Sarabhai Chemicals Ltd., Baroda.

© Brand of kanamycin sulphate by M/s Alembic Chemical Works Co. Ltd., Baroda.

©© Brand of thiopentone sodium by M/s May & Baker (India) Pvt. Ltd., Bombay.

RESULTS

RESULTS

Results obtained in the study are shown in Tables 1 to 12.

Surgical anaesthesia.

The average duration of surgical anaesthesia was 24.83 minutes in the control group, but this was prolonged to 39.6 minutes, 43.0 minutes and 50.8 minutes in group I dogs treated with chloramphenicol at 30 minutes, 60 minutes and 120 minutes respectively, prior to the administration of thiopentone sodium. The average duration of surgical anaesthesia in dogs treated with streptomycin at the same intervals were 35.0, 37.5 and 40.8 minutes. Similarly the dogs in group III which were treated with kanamycin in a similar manner were 30.8 minutes (batch A), 38.3 minutes (batch B) and 46.5 minutes (batch C).

Sleeping time.

The average duration of sleeping time in control group was 66.5 minutes, whereas it was 91.5 minutes, 95.0 minutes and 108.1 minutes in group I dogs (treated with chloramphenicol), 87.5 minutes, 92.3 minutes and 98.8 minutes in group II dogs (treated with streptomycin) and 78.8 minutes, 85.3 minutes and 106.6 minutes in

group III dogs (treated with kanamycin).

PCV and ESR values.

None of the drugs produced any significant difference in the PCV and ESR values.

DISCUSSION

DISCUSSION

After most surgical procedures conducted under general anaesthesia, the patient should recover from the anaesthesia as rapidly as possible. If the period of non-ambulation is markedly prolonged, certain complications may develop that may prove detrimental to the patients recovery. The recovery phase of the barbiturate anaesthesia is known to produce anxiety and ataxia in animals. Excessive prolongation of this period may increase the chance of self inflicted trauma (Adams and Dixit, 1970).

Prophylactic administration of chloramphenicol prior to surgical procedures has been recommended in dogs and man (Bernard and Cole, 1964).

It has been suggested that higher doses of antibiotics may be essential to treat certain conditions that may be encountered in conjunction with surgery (Adams, 1970). In the present study high doses of chloramphenicol (50 mg/kg body weight) in dogs produced a prolongation in the mean duration of thiopentone sodium anaesthesia and sleeping time than in the control group.

Experimental evidence indicated that chloramphenicol inhibits the activity of liver microsomal enzymes (Dixon

and Fouts, 1962). *In vitro* studies with mouse liver microsomal fractions have shown the inhibition of the metabolism of hexobarbitone, codeine, aminopyrine and acetanilid by chloramphenicol (Adams, 1970 and Adams and Dixit, 1970).

Recent studies in man had shown the retardation of biotransformation of Diphenylhydantoin, dicoumarol, tolbutamide *in vivo* by chloramphenicol (Christensen and Skovsted, 1969). This evidence suggests that the prolongation of pentobarbitone anaesthesia observed in dogs by the early workers was the result of inhibition of activity of liver microsomal enzymes that inactivates pentobarbitone by 3'-C hydroxylation (Adams, 1970; Adams and Dixit, 1970).

It has also been suggested that chloramphenicol inhibits microsomal enzymes in the liver of rabbits, which enhanced the activity of barbiturate narcosis (Gibasiewicz and Gibasiewicz, 1976).

Brodie and associates (1955) have identified the enzyme system in the microsomas of rat liver cells which are responsible for inactivation of barbiturates and these required both reduced triphosphopyridine nucleotide (TPNH) and oxygen. They are responsible for side chain oxidation of hexobarbitone, pentobarbitone and thiopentone.

In experimental animals surgical removal of the liver or severe hepatic injury induced by poisons greatly prolonge

the duration of anaesthesia by large doses of all barbiturates except barbitone (Maynert, 1971).

Chloramphenicol did not prolong the duration of anaesthetic action of barbitone which is not extensively metabolised by the liver, but is excreted relatively unchanged in the urine (Booth, 1965 and Krantz Jr. and Carr, 1969).

Adams (1970) found a 12 per cent increase in the duration of pentobarbitone anaesthesia in dogs, when Chloramphenicol (33 mg/kg body weight) was given immediately before the administration of pentobarbitone. He reported that this effect was due to the inactivation of liver microsomal enzymes by chloramphenicol.

Using sodium pentobarbitone Nash et al. (1956) noticed a decrease in the packed cell volume (PCV) during the first hour of anaesthesia in dogs and then a slow recovery. A transient fall in PCV with sodium pentobarbitone anaesthesia was reported by Graca and Grant (1957) in dogs. Benjamin (1961) showed that pentobarbitone anaesthesia induced a transient fall in total red blood cells, haematocrit and haemoglobin values.

The prolongation in the thiopentone induced surgical anaesthesia and sleeping time by the prior administration of chloramphenicol observed in the present study is in

partial agreement with Adams (1970), who reported in dogs a 12 per cent increase in surgical anaesthesia induced by pentobarbitone. According to Laurance (1973) barbiturates are metabolised chiefly by the liver and hence prior administration of chloramphenicol may inhibit the metabolism of thiopentone in a similar manner to that of pentobarbitone, by interfering with the hepatic microsomal enzyme. The PCV and ESR values were not effected by these drugs in the current study.

Administration of streptomycin and kanamycin in the present study had only slight effect in the duration of anaesthesia and sleeping time in dogs and does not show any influence on PCV and ESR values. Relevant reports on the action of streptomycin and kanamycin in the respect are scanty and it is presumed that both these antibiotics may be acting by inhibiting liver microsomal enzymes in a lesser extent and similar manner to that of chloramphenicol.

TABLES AND ILLUSTRATIONS

Table 1. Duration of surgical anaesthesia, sleeping time, PCV and ESR values of the control dogs.

Number	Body weight (kg)	Amount of thiopentone (mg)	Sleeping time (minutes)	Surgical anaesthesia (minutes)	PCV (%)		ESR mm/hr	
					Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
1	7.0	210	65	25	48	47	0	1
2	8.5	255	55	25	65	63	0	0
3	10.5	315	70	26	40	40	0	0
4	8.2	246	54	24	48	48	0	0
5	9.5	285	80	27	40	39	1	2
6	8.5	255	75	22	50	49	0	0
Total			399	149				
Average			66.5	24.8				

* given only thiopentone sodium as 2.5% solution @ 30 mg/kg.

Table 2. Duration of surgical anaesthesia, sleeping time, PCV and ESR values of dogs treated with chloramphenicol (50 mg/kg) 30 minutes prior to the administration of thiopentone sodium.

Number	Body weight (kg)	Amount of chloram-phenicol (mg)	Amount of thiopentone (mg)	Sleeping time (minutes)	Surgical Anaesthesia (minutes)	PCV (%)		ESR mm/hr	
						Pre treat-ment	Post treat-ment	Pre treat-ment	Post treat-ment
1	9.5	475	285	85	38	50	48	0	1
2	7.5	375	225	92	40	48	46	0	0
3	8.2	410	246	102	45	39	39	3	4
4	10.2	510	306	105	50	46	45	0	0
5	8.0	400	240	75	30	36	36	2	2
6	10.0	500	300	90	35	45	45	0	0
Total				549	238				
Average				91.5	39.6				

Table 3. Duration of surgical anaesthesia, sleeping time, PCV and ESR values of dogs treated with chloramphenicol (50 mg/kg) 60 minutes prior to the administration of thiopentone sodium.

Number	Body weight (kg)	Amount of chloram-phenicol (mg)	Amount of thiopentone (mg)	Sleeping time (minutes)	Surgical anaesthesia (minutes)	PCV (%)		ESR mm/hr	
						Pre treat-ment	Post treat-ment	Pre treat-ment	Post treat-ment
1	10.5	525	315	70	35	52	51	0	0
2	8.5	425	255	115	45	50	46	0	1
3	10.5	525	315	80	50	48	48	0	0
4	9.5	475	285	110	52	38	37	0	0
5	8.0	400	240	105	40	46	44	2	4
6	9.2	460	276	90	36	42	42	0	0
Total				570	258				
Average				95.0	43.0				

Table 4. Duration of surgical anaesthesia, sleeping time, PCV and ESR values of dogs treated with chloramphenicol (50 mg/kg) 120 minutes prior to the administration of thiopentone sodium.

Number	Body weight (kg)	Amount of chloram-phenicol (mg)	Amount of thiopentone (mg)	Sleeping time (minutes)	Surgical anaesthesia (minutes	PCV (%)		ESR mm/hr	
						Pre treat-ment	Post treat-ment	Pre treat-ment	Post treat-ment
1	10.5	525	315	122	50	38	36	4	3
2	10.3	515	309	95	48	58	56	0	0
3	8.0	400	240	103	55	49	49	0	1
4	7.5	375	225	95	40	50	48	1	2
5	9.0	450	270	140	60	39	37	0	0
6	9.0	450	270	94	52	45	45	0	0
Total				649	305				
Average				108.1	50.8				

Table 5. Duration of surgical anaesthesia, sleeping time, PCV and ESR values of dogs treated with streptomycin (10 mg/kg) 30 minutes prior to the administration of thiopentone sodium.

Number	Body weight (kg)	Amount of streptomycin (mg)	Amount of thiopentone (mg)	Sleeping time (minutes)	Surgical anaesthesia (minutes)	PCV (%)		ESR mm/hr	
						Pre treatment	Post treatment	Pre treatment	Post treatment
1	8.4	85	162	90	25	55	54	0	0
2	11.7	115	351	95	42	58	56	1	3
3	10.0	100	300	110	45	45	45	0	1
4	8.0	80	240	85	38	43	43	2	4
5	11.0	110	330	75	35	48	47	0	0
6	10.0	100	300	70	25	36	36	0	0
Total				525	210				
Average				87.5	35.0				

Table 6. Duration of surgical anaesthesia, sleeping time, PCV and ESR values of dogs treated with streptomycin (10 mg/kg) 60 minutes prior to the administration of thiopentone sodium.

Number	Body weight (kg)	Amount of streptomycin (mg)	Amount of thiopentone (mg)	Sleeping time (minutes)	Surgical anaesthesia (minutes)	PCV (%)		ESR mm/hr	
						Pre treatment	Post treatment	Pre treatment	Post treatment
1	8.7	90	260	75	32	45	44	1	1
2	7.5	75	225	105	40	32	32	0	0
3	9.0	90	270	96	38	55	50	2	1
4	10.0	100	300	80	30	52	52	5	4
5	8.5	85	255	98	40	38	36	0	0
6	9.5	95	285	100	45	40	40	0	0
Total				554	225				
Average				92.3	37.5				

Table 7. Duration of surgical anaesthesia, sleeping time, PCV and ESR values of dogs treated with streptomycin (10 mg/kg) 120 minutes prior to the administration of thiopentone sodium.

Number	Body weight (kg)	Amount of streptomycin (mg)	Amount of thiopentone (mg)	Sleeping time (minutes)	Surgical anaesthesia (minutes)	PCV (%)		ESR mm/hr	
						Pre treatment	Post treatment	Pre treatment	Post treatment
1	13.5	135	405	110	45	37	35	0	1
2	9.8	100	295	98	40	52	49	0	0
3	11.5	115	345	90	38	46	42	0	0
4	9.0	90	270	85	42	55	52	3	2
5	7.8	80	235	95	30	32	32	0	0
6	8.4	85	250	115	50	50	50	0	0
Total				593	245				
Average				98.8	40.8				

Table 8. Duration of surgical anaesthesia, sleeping time, PCV and ESR values of dogs treated with kanamycin (10 mg/kg) 30 minutes prior to the administration of thiopentone sodium.

Number	Body weight (kg)	Amount of kanamycin (mg)	Amount of thiopentone (mg)	Sleeping time (minutes)	Surgical anaesthesia (minutes)	PCV (%)		ESR mm/ht	
						Pre treatment	Post treatment	Pre treatment	Post treatment
1	7.8	80	235	70	27	40	38	0	0
2	8.0	80	240	95	28	42	42	0	1
3	12.0	120	360	65	30	38	36	0	0
4	9.5	95	285	85	35	46	45	2	2
5	9.0	90	270	98	40	39	39	0	0
6	8.2	85	245	60	25	35	35	1	0
Total				473	185				
Average				78.8	30.8				

Table 9. Duration of surgical anaesthesia, sleeping time, PCV and ESR values of dogs treated with kanamycin (10 mg/kg) 60 minutes prior to the administration of thiopentone sodium.

Number	Body weight (kg)	Amount of kanamycin (mg)	Amount of thiopentone (mg)	Sleeping time (minutes)	Surgical anaesthesia (minutes)	PCV (%)		ESR mm/hr	
						Pre treatment	Post treatment	Pre treatment	Post treatment
1	9.0	90	270	80	37	42	41	1	2
2	7.5	75	225	92	35	38	37	0	0
3	8.0	80	240	70	40	48	48	0	0
4	9.0	90	270	78	36	36	34	4	2
5	11.5	115	345	90	40	50	49	0	0
6	13.5	135	405	102	42	46	46	2	1
Total				512	230				
Average				85.3	38.3				

Table 10. Duration of surgical anaesthesia, sleeping time, PCV and ESR values of dogs treated with kanamycin (10 mg/kg) 120 minutes prior to the administration of thiopentone sodium.

Number	Body weight (kg)	Amount of kanamycin (mg)	Amount of thiopentone (mg)	Sleeping time (minutes)	Surgical anaesthesia (minutes)	PCV (%)		ESR mm/hr	
						Pre treatment	Post treatment	Pre treatment	Post treatment
1	11.5	115	345	102	35	53	53	2	3
2	8.5	85	255	95	40	35	33	0	0
3	8.0	80	240	100	47	48	46	0	1
4	7.8	80	235	118	52	52	50	0	0
5	9.5	95	285	115	55	45	42	0	2
6	9.0	90	270	110	50	38	38	0	0
Total				640	279				
Average				106.6	46.5				

Table 11. Analysis of variance table for surgical anaesthesia in dogs.

Source of variation	df	SS	MSS	F
Between treatments	2	486.77	243.39	5.62**
Between periods	2	1079.11	539.56	12.47**
Error	49	2120.95	43.28	
Total	53	3686.83		

** significant at 5% and 1% levels.

Pairwise comparison:

M1-M2 = 44.50-37.78 = 6.72
M2-M3 = 37.78-38.56 = -0.78

Table 12. Analysis of variance table for sleeping time in dogs.

Source of variation	df	SS	MSS	F
Between treatments	2	590.26	295.13	1.56
Between periods	2	3345.59	1672.80	8.82**
Error	49	9290.91	189.61	
Total	53	13226.76		

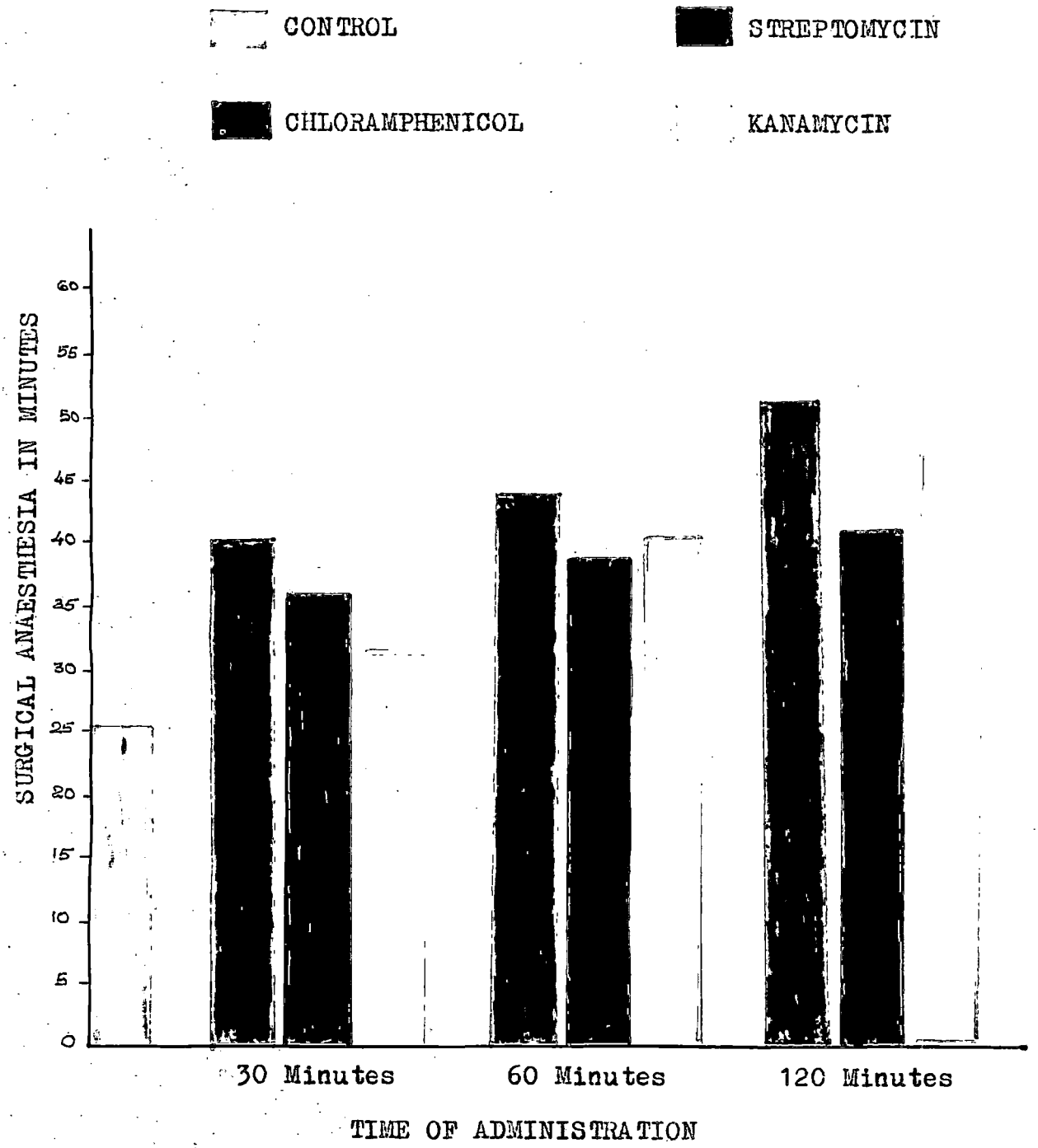
** significant at 5% and 1% levels.

Pairwise comparison:

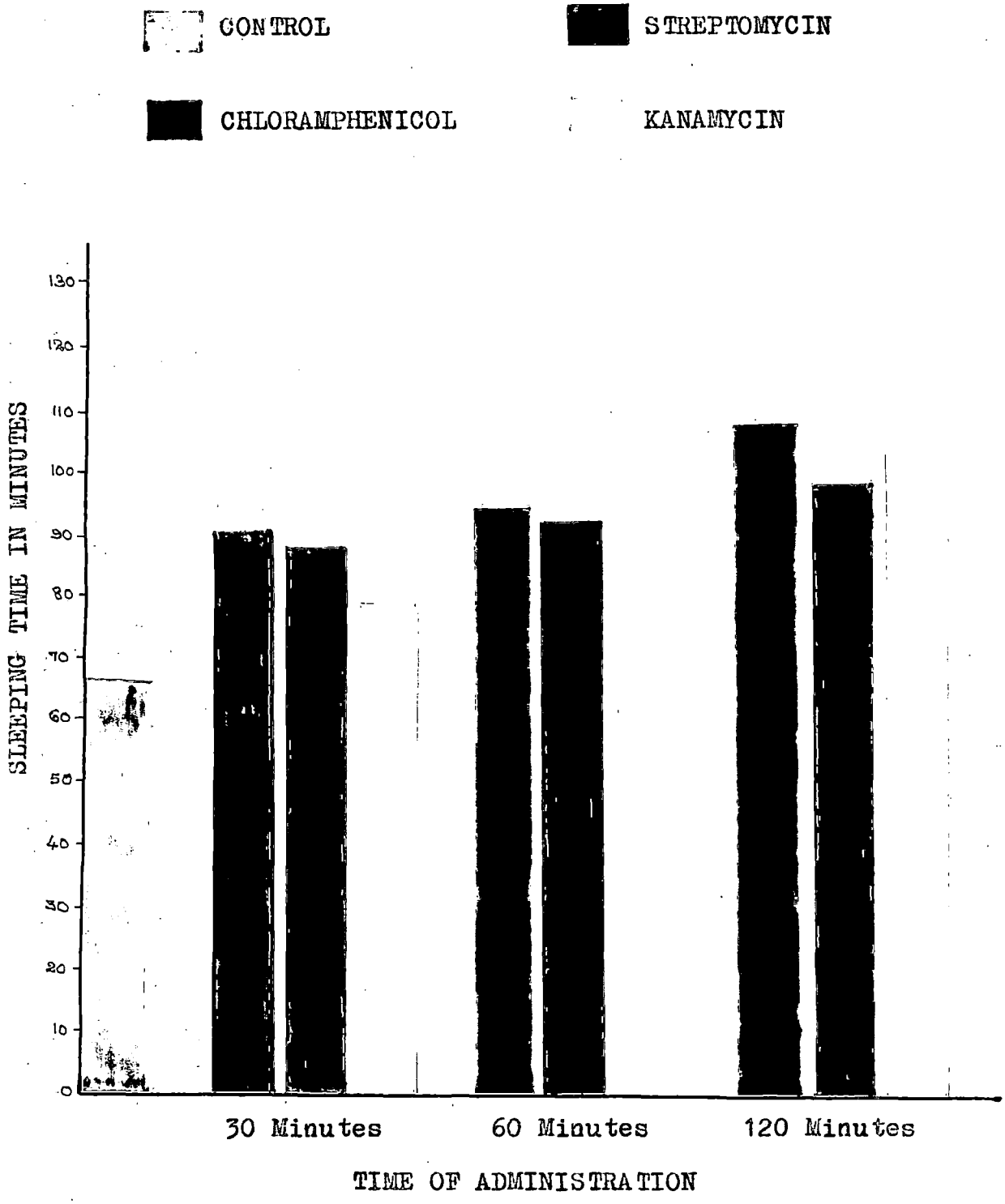
M1-M2 = 98.22-92.89 = 5.33

M2-M3 = 92.89-90.28 = 2.61

EFFECT OF PRIOR ADMINISTRATION OF CHLORAMPHENICOL, STREPTOMYCIN AND KANAMYCIN ON SURGICAL ANAESTHESIA DURING THIOPENTONE SODIUM ANAESTHESIA IN DOGS.



EFFECT OF PRIOR ADMINISTRATION OF CHLORAMPHENICOL, STREPTOMYCIN AND KANAMYCIN ON SLEEPING TIME DURING THIOPENTONE SODIUM ANAESTHESIA IN DOGS.



SUMMARY

SUMMARY

Based on the studies on the influence of chloramphenicol, streptomycin and kanamycin on thiopentone sodium anaesthesia in dogs the following conclusions were made:

1. The average duration of surgical anaesthesia and sleeping time in the control group produced by the administration of thiopentone sodium intravenously at the rate of 30 mg/kg body weight were 24.8 minutes and 66.5 minutes respectively.

2. Administration of chloramphenicol at the rate of 50 mg/kg body weight intramuscularly, 30 minutes prior to thiopentone sodium injection, enhanced the average duration of surgical anaesthesia and sleeping time to 36.6 minutes and 91.5 minutes respectively.

3. The duration of surgical anaesthesia and sleeping time, when chloramphenicol administered at the same dose intramuscularly, 60 minutes prior to the administration of thiopentone sodium were 43.0 minutes and 95.0 minutes respectively.

4. Chloramphenicol, when administered at the same dose and route, 120 minutes prior to thiopentone

sodium injection produced an average of 50.8 minutes surgical anaesthesia and 108.1 minutes sleeping time.

5. Administration of streptomycin at the rate of 10 mg/kg body weight as detailed above, produced surgical anaesthesia for a period of 35.0, 37.5 and 40.8 minutes and sleeping time of 87.5, 92.3 and 98.8 minutes.

6. Similarly administration of kanamycin at a dose of 10 mg/kg body weight in the same pattern resulted in the production of surgical anaesthesia for 30.8, 38.8 and 46.5 minutes and sleeping time for 78.8, 85.3 and 106.6 minutes.

7. Neither thiopentone sodium nor its administration along with chloramphenicol, streptomycin or kanamycin had any influence on the PCV and ESR values.

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STUDIES ON THE INFLUENCE OF CHLORAMPHENICOL ON THIOPENTONE SODIUM ANAESTHESIA IN DOGS

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ABSTRACT OF A THESIS

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ABSTRACT

A study was undertaken to find out the influence of chloramphenicol, streptomycin and kanamycin on thiopentone sodium anaesthesia in dogs. Chloramphenicol 50 mg/kg body weight, streptomycin 10 mg/kg body weight and kanamycin 10 mg/kg body weight were administered intramuscularly at 30, 60 and 120 minutes prior to the administration of thiopentone sodium, which was given at the rate of 30 mg/kg body weight intravenously.

These antibiotics (chloramphenicol, streptomycin and kanamycin) produced a slight prolongation in the surgical anaesthesia and sleeping time, induced by thiopentone sodium Chloramphenicol showed a significant effect over the other two drugs in these respects. It was also noticed that neither thiopentone sodium nor its administration along with chloramphenicol, streptomycin and kanamycin does possess any influence on the PCV and ESR values.