STUDIES ON THE MANAGEMENT OF CARDIOPULMONARY DYSFUNCTION DUE TO THIOPENTONE ANAESTHESIA IN THE BOVINE

By

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M.V.Sc.

A

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(P.K.PESHIN)

CERTIFICATE I

This is to certify that this dissertation entitled, "Studies on the management of cardiopulmonary dysfunction due to thiopentone anaesthesia in the bovine" submitted for the degree of Ph.D., in the subject of Veterinary Surgery and Radiology of the Haryana Agricultural University, is a bonafide research work carried out by Dr.P.K.Pashin under my supervision and that no part of this dissertation has been submitted for any other degree.

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CERTIFICATE II

This is to certify that the dissertation entitled, "Studies on the management of cardiopulmonary dysfunction due to thiopentone anaesthesia in the bovine" submitted by Dr.P.K.Peshin to the Haryana Agricultural University in partial fulfilment of the requirements for the degree of Ph.D., in the subject of Veterinary Surgery and Radiology has been approved by the Student's Advisory Committee after an oral examination on the same, in collaboration with an External Examiner.

Major Adviser 8/9/86

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C O N T E N T S

Chapter		Page
I.	INTRODUCTION	1-4
II.	REVIEW OF LITERATURE	5-16
III.	MATERIALS AND METHODS	17-24
IV.	RESULTS	25-69
V.	DISCUSSION	70-99
VI.	SUMMARY AND CONCLUSION	100-105
VII.	LITERATURE CITED	106-117

INTRODUCTION

Human cardiopulmonary resuscitation has undergone tremendous advances over the last two decades. A number of factors contribute towards cardiac or respiratory arrest or embarrassment, where proper medical attention can save the life of the patient. In veterinary practice, small animals alone have received adequate attention in this direction. Application of the required treatment and the facilities needed for the management of cardiac arrest, however, may not be routinely possible in large animal practice. Nevertheless, quite frequently a situation could arise when cardiopulmonary embarrassment may occur which if effectively managed may save the life of the patient.

Resuscitation has been described as the revival of life, by using methods, medicines, procedures or techniques so as to restore the health of unconscious or apparently dead patient (Ross and Brennock, 1981). Successful resuscitation depends not only on the knowledge or skill of the practitioner, but also on the speed with which it is applied. Severely embarrassed respiration warrants immediate attention as respiratory abnormality because of hypoxia can promptly lead to cardiac embarrassment. Although, theoretically cardiac and respiratory emergency managements are described individually; yet in a clinical case both conditions require immediate and simultaneous

attention. A patent airway with adequate oxygenation is a prerequisite for cardiac resuscitation. Therefore, management of respiratory failure assumes great significance in large animal practice.

Common causes of cardiopulmonary embarrassment during surgery are anaesthetic overdose, hypersensitivity to anaesthetics or preanaesthetics or iatrogenic problems. The most serious outcome in such cases follows overdosage with barbiturates. Since blood pH dictates the degree of dissociation of barbiturates in blood and their ability to penetrate the cell wall, respiratory acidosis promotes the entrance of the barbiturate into the brain cells to depress the cardiac and respiratory centres further.

Although local or regional analgesia is preferred in large ruminants due to their inherent unsuitability for general anaesthetics, the latter is frequently required for a number of surgical operations. Despite considerable advancement in the use of inhalant anaesthetics, barbiturates are still used to induce or to maintain anaesthesia in cattle. This is so because of their ease of administration, economic consideration and easy availability. Frequently barbiturate administration in cattle and buffaloes cause cardiopulmonary embarrassment of serious order. Management of such medical emergencies in large animal practice remains empirical because of

lack of information on the effects or efficacy of various drugs in cattle and buffaloes. Work on non-inhalant and inhalant anaesthetics in recent years has shown that the response in buffaloes differs much from that in other species. The buffaloe heart also has a predominance of parasympathetic system (Gopakumar, 1977). The response of buffaloes to various drugs that may be used to correct cardiopulmonary embarrassment is not predictable.

Therefore a large gap exists in the knowledge concerning the effects of various drugs which may be used to correct cardiopulmonary embarrassment in the buffalo. Initially each drug needs to be evaluated singly, irrespective of its stimulating effect on the cardiac or respiratory system. Combinations of drugs will also have to be tried to stimulate both cardiac and respiratory system simultaneously. Guidelines on these aspects, will certainly go a long way in making anaesthetic procedures and subsequent surgery safer for the animal. The therapeutic utility of various pressor amines, respiratory stimulants and massive doses of corticosteroids has been stressed from time to time in men, dogs, and laboratory animals. However, no study in this regard in bovines is available.

Keeping in view the above considerations the present study was conducted on buffalo calves with the

following objectives:

1) to create cardiopulmonary dysfunction in buffalo calves with thiopentone to study their nature.
2) to compare the effects of certain drugs for the management of cardiopulmonary dysfunction during anaesthesia; and
3) to make an attempt to evolve a management schedule for overcoming cardiopulmonary dysfunction during anaesthesia.

REVIEW OF LITERATURE

Thiopentone sodium is the only cheaply available intravenous general anaesthetic commonly used in human and veterinary practice in India. Its onset of anaesthetic effect after intravenous administration is rapid and duration is brief. Considerable work has been done on thiopentone in different species. Various experimental as well as clinical reports of thiopentone, used alone or in combinations, in buffaloes are available in the literature (Mirakhur et al., 1980; Singh et al., 1980; Nigam et al., 1983; Peshin and Nigam, 1985; Peshin et al., 1986). All are aware of its pharmacokinetic and pharmacodynamic limitations. Adverse drug reactions mostly go unreported. Ndiritu and Enos (1977) conducted a survey at school of Veterinary Medicine, California, to investigate the incidence of adverse drug reaction in animals. The records of 39541 animals were screened, of this 0.4% had one or the other adverse drug reaction. From those animals which had adverse drug reaction, 30% were due to anaesthetic agents. Perusal of the available literature did not reveal any such report regarding thiopentone in buffaloes, but it does not mean that adverse response to thiopentone in buffaloes does not occur. Chances of overdosage with thiopentone are more if one starts using it as a sole anaesthetic in a relatively time consuming

surgery. No study has so far been reported in the literature, which would describe efficacy of pharmacological management under such emergencies in buffaloes. Ferguson et al. (1978) have made it clear that when hypotension is severe it could quickly lead to the development of irreversible shock due to loss of regulation of vital processes from brain. Steen and Michenfelder (1979) are of the opinion that if respiratory and circulatory supports are instituted early enough and adequately maintained, cerebral recovery is expected even when EEG activity is initially absent. Dundee and Wyant (1974b) suggested that, to correct thiopentone induced prolonged hypotension, vasoconstrictors should be used. Besides effects of pressor amines and corticosteroids, considerable work done on other species to combat circulatory insufficiency or arrest appeared in the literature. Here in brief review of reports, related to our experiments is given in chronological order:

Hellerstein et al. (1952) used mephentermine in 18 human patients of cardiogenic shock. In this preliminary study, the drug was found to be a safe and effective pressor substance with little effect on myocardial irritability. Fourteen emerged from shock state with marked clinical improvement for more than two

days. Seven succumbed to secondary complications 2 to 26 days later. Seven patients recovered sufficiently to be discharged from the hospital.

Welsh et al. (1958) studied the effects of mephentermine in dogs. The drug produced a striking elevation of the ventricular function curve in the isolated supported dog heart and in the dogs with an open chest and a complete circulation. The drug appeared to have little effect on peripheral vascular resistance. Under controlled haemodynamic conditions the drug caused increased myocardial oxygen consumption.

Horsley and Eckstein (1961) evaluated the effects of mephentermine administration in dogs anaesthetised with pentobarbital and in those treated with gallamine. Observations were also made in normotensive animals and in the animals made hypotensive by intravenous hexamethonium. Mephentermine regularly caused an increase in cardiac output and arterial pressure regardless of the control state of the animal. It was concluded that mephentermine raised the arterial pressurelevel by increasing both cardiac output and peripheral resistance.

Palich and Gordon (1967) recommended sodium bicarbonate (25 ml of 7.5% solution) and 0.5 ml of 1:1000 epinephrine every 10 minutes, and after heart activity is returned 10 to 20 ml of 10% calcium gluconate during resuscitation efforts in dogs.

Moffitt et al. (1968) suggested that a drip of isoprotamenol is probably the best when patient can not maintain a satisfactory arterial pressure due to failing myocardium. This drug provides only beta-receptor stimulation with satisfactory increase in cardiac output, better peripheral perfusion, less ventricular irritability and less stimulation of central nervous system than epinephrine. Although epinephrine has similar effects but simultaneous vasoconstriction in the kidney and skin also occurs.

Short et al. (1968) used successfully phenylephrine HCl (5 to 10 mg as 1 mg/ml solution) and atropine sulphate (0.2 to 0.8 mg/100 kg) to overcome hypotension and bradycardia, respectively, in a series of 100 calves subjected to cardiac surgery. Lignocaine (200 mg/kg) and procaine amide HCl (200 to 600 mg/100 kg) were used to control ventricular arrythmias. Calcium chloride (1 g/100 kg) was effective to correct poor myocardial tone.

Bagwell and Daniell (1970) evaluated the comparative effects of norepinephrine and dopamine following induced cardiogenic shock in dogs. Although dopamine increased the myocardial oxygen consumption relatively greater, both drugs were found to have equal efficacy. It was suggested that dopamine should be particularly useful in patients with extremely low blood pressure where immediate elevation of coronary perfusion is felt necessary to sustain life.

According to Moran (1970) mephentermine primarily stimulates heart at doses that produce little effect on peripheral vessels. High doses cause dilatation in renal, splanchnic and femoral vascular beds. Since the doses needed to produce vasodilatation are far higher than that required for cardiac stimulation, the vasodilating action may have little clinical importance.

Grinstein-Nadler and Bottoms (1976) evaluated dexamethasone treatment following haemorrhagic shock in dogs. Dexamethasone was used at the dose rate of 5 mg/kg. At the onset of injection, blood pressure increased and urine output was restored. Dexamethasone treatment was shown to prevent extracellular fluid volume from decreasing below the amount due to plasma lost during haemorrhage. Also some membrane transport mechanism was maintained near normal.

Kumar and Bahga (1976) observed that intravenous administration of epinephrine (25 µg/kg) increased the serum potassium and packed cell volume in buffalo calves. The inorganic phosphorus, calcium and sodium values were not affected. Pretreatment with phentolamine (1 mg/kg) did not block the epinephrine induced effects on serum potassium and packed cell volume.

Mephentermine was found to have a similar action as that of epinephrine by Ogborn (1976). Much of its action was attributed to augumentation of myocardial

contractility and cardiac output instead of vasoconstriction. Tachyphylaxis occurred readily with repeated doses.

Anderson and Aitken (1977) evaluated the effects of catecholamine administration in the horses. Adrenaline administration increased blood levels of glucose, lactate, free fatty acids, and glycerol. A similar effect on glucose level was produced by noradrenaline but not by isoprenaline. Pretreatment with propranolol did not prevent this response to adrenaline.

Clark (1977) stated that therapeutic goal of drugs affecting heart and to be used in cardiac resuscitation should include improved conduction, enhanced contractability, decreased irritability and increased threshold for defibrillation. Epinephrine stimulates pacemaker discharge and has positive inotropic action. However, it also induces ventricular fibrillation. This effect can be reduced by intravenous preadministration of lignocaine (1-2 ml/kg).

Jenkins and Clark (1977) reviewed the drugs affecting heart. The use of potent cardiac stimulants like epinephrine, norepinephrine, isoproterenol and dopamine by intracardiac injection was not recommended because of their pro-fibrillatory property. Glucocorticoids have minor cardiotonic actions which alongwith the proposed lysosomal stabilisation action in large doses should be beneficial.

Lappas et al. (1977) advocated the use of isoproterenol in patients with slow heart rates and low cardiac output, because of electrophysiological effects of the drug on the heart. An initial dose of 1 to 1.5 µg/minute as an infusion was recommended with cautious approach as drug may cause tachycardia, ventricular arrhythmias and hypotension. The use of epinepharine was recommended in cases of hypotension and low cardiac output due to impaired cardiac function rather than due to hypovolemia. A combination of norepinepharine and phentolamine was advocated in states of low cardiac output, because of the ability of phentolamine to obviate adverse effects of vasoconstriction caused by norepinepharine.

According to Lucchesi (1977) dopamine, by acting on beta receptors in heart, stimulates an increase in myocardial contractility, this causes an increased stroke volume and cardiac output without increase in heart rate. Generally tachyarrhythmia is not produced and peripheral vascular resistance remains stable. Blood flow to some vascular beds may decrease but mesenteric and renal blood flow increases.

Lucke and Waterman (1977) listed four steps to overcome cardiopulmonary emergencies in veterinary practice. They include, establishment of an air way, ventilation of the lungs, cardiac massage alongwith use of various drugs

and intravenous infusion with correction of acidosis. For persistant asystole, an injection of 1 to 5 ml of calcium gluconate (10%) into the left ventricle was recommended. In case of failure 0.5 to 3.0 ml of adrenaline (1:10,000) given i.v. was recommended to induce myocardial contraction.

Muir (1977) investigated the effects of changes in heart rate due to thiamylal induced bigeminy in dogs. Results showed that most dysarrhythmias in dogs during thiobarbiturate anaesthesia appear to occur due to an imbalance between parasympathetic and sympathetic efferent activity. Atropine was effective in abolishing ventricular bigeminy in most cases. Propranolol appeared to abolish ventricular bigeminal rhythms by suppression of sympathetic efferent activity without causing noticeable changes in arterial blood pressure.

Remakhani et al. (1977) investigated the effects of epinephrine (5 µg/kg) in 10 unanaesthetised sheep. All animals developed serious arrhythmias. The sheep anaesthetised with thiopentone and thiopentone-halothane combination developed arrhythmias of the order of 10 and 80% respectively. A challenge injection of epinephrine (5 µg/kg) in sheep anaesthetised with thiopentone also produced serious arrhythmias. However, arrhythmic doses of epinephrine did not produce serious arrhythmias when animals were premedicated with acepromazine maleate (0.5 mg/kg).

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Ferguson et al. (1978) showed that intravenous administration of dexamethasone (5 mg/kg) to dogs following haemorrhagic shock caused improved blood pressure and blood flow in the lungs, kidney and gastrointestinal tract. There was less cell damage as indicated by amounts of plasma enzymes released from damaged tissues. These effects favoured the maintenance of homeostatic state and greater chance for the survival of dogs.

Gilroy et al. (1980) subjected 17 adult Cynamolgus monkeys to potassium chloride- induced cardiopulmonary arrest of 10 to 12 minutes. The animals were resuscitated by means of oxygen, external cardiac massage, epinephrine, calcium and bicarbonate. The mean time required for resuscitation was 140 ± 70 seconds. Pupillary response and EEG were slow to return, with mean intervals of 90±85 and 108 ± 36 minutes respectively. Only 9 survived for 96 hours or more and only two were neurologically normal.

Ross and Bremnock (1981) advocated the use of hydrocortisone in resuscitation, because during cardiopulmonary arrest animal is certainly in "shock". It was felt that to get their maximum beneficial effects, corticosteroids should be used early and given in readily available form in high doses.

Mirakhur et al. (1982) studied the effects of thiopentone anaesthesia on plasma catecholamines and

cortisol levels in buffalo calves. The thiopentone sodium (8%) was administered "to effect". The adrenaline and noradrenaline increased significantly 30 to 60 minutes after anaesthesia while the increase in cortisol was not significant. The study indicated enhanced sympathetic activity during thiopentone anaesthesia in buffaloes.

Mielke and Klopzig (1985) evaluated electrocardiographic changes following intravenous administration (1 to 2 mg/animal) of adrenaline and noradrenaline in cattle. Both the drugs modulated the heart rate similarly. Initial moderate transient increase in heart rate was followed by a somewhat protracted phase of bradycardia. Catecholamine-dependent decline in heart rate could be prevented by preadministration of atropine. Typical T-wave variations tended to be stimulated by adrenaline and noradrenaline. Diphasic, rarely negative T-waves were found to occur soon after injection.

Ventilatory failure

Because of the relative ease with which an excessively deep plane of anaesthesia may be induced with thiopentone, the management of ventilation becomes important. Although circulatory insufficiency would be generally associated with ventilatory failure, but reverse may not hold true always. Booth (1982a) in this connection writes that pentobarbitone at a dose approximately four times that producing respiratory arrest may be administered before

cardiac arrest occurs in the artificially ventilated animal. How far this holds true for buffaloes needs to be seen. Needless to emphasise that the most urgent and crucial requirement in apneic patient would be restoration of ventilation. Pulich and Gordon (1967) emphasised, that ventilatory failure if exceeds 4 to 6 min, serious brain damage can be expected.

Prethamide acts directly on respiratory centers while nikethamide would also act through carotid and aortic bodies (Atkinson et al., 1977). Would these drugs restore ventilation in buffaloes having their respiratory centers depressed with thiopentone, need to be seen.

Cairy et al. (1961) induced ventilatory insufficiency with pentobarbitone in dogs and then evaluated effects of different drugs. There was not only different amounts of increase in ventilation, but also variety of patterns in these increases were observed. Their finding suggested that combination of drugs to increase ventilation may be useful. In order of increasing effectiveness in increasing ventilation in deeply anaesthetised dogs, the drugs as tested are: nikethamide, caffeine and sodium benzoate, metaraminol bitartrate, pentylenetetrazol, amphetamine sulphate, methethamide ^{2} in aqueous solution (0.8%) and methetharimide in prophylene glycol (3.0%).

Reynolds (1982) described prethcamide (C-8868) as respiratory stimulant to be used in the treatment of respiratory insufficiency. It can be given orally, intramuscularly, slow intravenously or by slow infusion. Side effects include: headache, paraesthesia, restlessness, muscular twitching, tremors, dyspnoea and flushing of the skin. He emphasised that prethcamide be used with care in patients with epilepsy.

MATERIALS AND METHODS

Studies were done on 40 apparently healthy male buffalo calves (Bubalus bubalis) of one and half to two years and weighing between 55 to 120 kg. All animals were kept under standard managemental conditions having free access to feed and water. They were randomly divided in eight groups of five animals each. In each group following drugs were evaluated after induction of cardiopulmonary dysfunction;

Group I - Acted as control. No drug was used.

Group II - Mephentermine[1].

Group III- Norepinephrine[2].

Group IV - Dexmethasone[3].

Group V - Prethemide[4].

1- Mephentine: Mephentermine sulphate I.P. having mephentermine base as 30 mg/ml. John Wyeth and Brother Ltd., Steelcrete House, Dinshaw Wacha Road, Bombay-400 020, India.

2- Nor-drin: Norepinephrine bitartrate USP, 2 mg/ml (equivalent to 1 mg of norepinephrine base). Unichem Laboratories Ltd., S.V.Road, Jogeshwari,Bombay, India.

3- Restimulen : Prethemide, 150 mg/ml. S.C.Pharmaceuticals, Ranoli, Dist.Baroda, Gujarat, India.

4- Cormine: Nikethamide, 25%, Ciba of India Ltd., Bombay-20, India.

Group VI - Nikethamide[5].

Group VII- Mephentermine and prethcamide.

Group VIII-Norepinephrine and nikethamide.

All calves were fasted for a day before initiation of the experiments. Calves were restrained comfortably in right lateral recumbency and the area in the neck and on the forehead was prepared before starting the experiment. Carotid artery and jugular vein were exteriorised under local analgesia (Lignocaine HCl)[6] with least disturbance to the vagus nerve, and catheters were placed in position.

The arterial catheter was connected through a three-way stop-cock to the strain gauge pressure transducer which fed signals to multichannel recorder[7]. The amplifier was calliberated for 0 to 26.6 kPa (0 to 200 mmHg) to record arterial pressure. The venous catheter was also connected through a three-way stop-cock to a water manometer for measuring central venous pressure (CVP). The position of venous catheter in the cranial vena cava was confirmed by assuring synchronisation of water level fluctuations with respiratory movements. Reference level of manometer was set at the level of sternal manubrium with the help of a

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5- Wymesone: Dexamethasone sodium phosphate IP (Dexamethasone 21-phosphate) 4 mg/ml. Wyeth Laboratories Ltd., Steelcrete House, Dinshaw Wacha Road, Bombay-400 020, India.

6- Gesicaine: Lignocaine hydrochloride (2%) S.G.Chemicals and Pharmaceuticals, Kanoli, Dist.Baroda, Gujarat, India.

7- Polyrite and Polyvision: Recorders and Medicare System, 181/5, Phase-I, Industrial Area, Chandigarh-160 002, India.

spirit level. The manometer was filled with heparin-saline solution (10 units/ml) between measurements. Before taking the reading the manometer heparin-saline reservoir was turned full on and manometer filled and then stopped. When the stepwise fluid level fall ceased, CVP recording was made.

The electrocardiogram (ECG) was recorded using bipolar base-apex lead. Designated positive needle electrode was inserted at the lower thorax at cardiac apex, and negative electrode at upper one third of the right scapula. Recordings were made on another channel of multichannel recorder. Additionally, leads were connected to Patient bedside monitor[8] to observe the heart rate and ECG display.

For electroencephalogram (EEG), the designated positive and negative needle electrodes were inserted subcutaneously below the base of the horn about 2 cm left and right, lateral to the median frontline respectively. The EEG was also recorded on the multichannel recorder with signal output of the amplifier 75 μV/cm with 50 Hz cut, 0.5 TC and paper speed of 25 mm/s.

Rectal temperature and respirations per minute were

8- Patient Bedside Monitor; CMP-1131, British Physical Laboratories, India Pvt.Ltd., 32-Church Street, Bangalore-560001; 304-Ashok Bhavan, 93- Nehru Place, New Delhi-110 019, India.

recorded with Patient bedside monitor using thermister transducers.

In four groups, the respiratory minute volume was determined using a drum type expirograph.

Arterial and venous blood samples were collected haematically in heparinised syringes and analysed for pCO_2 and pO_2 with a blood gas analyser[9] at 37°C. The venous blood samples were also collected for determination of blood haemoglobin (Cynmethaemoglobin method), blood glucose (Folin and Wu, 1920), total proteins (Biuret method), and plasma creatinine (Folin and Wu, 1919).

All parameters, except for blood tests were monitored continuously on visual devices. About one hour was allowed after catheterisation of vessels for stabilisation of parameters which were then recorded (except minute volume) to form base (0 hr) values. After this, 5% thiopentone sodium[10] was administered 'to effect' in the ear vein and animals were intubated.

In animals of groups I, II, III and IV i.e. control group and where hypotension was induced and subsequently nephentermine, norepinephrine and dexamethasone evaluated,

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9. Radiometer: The BMK 33, Microequipment, Radiometer A/S. Emdrupvej 72.DK 2400. Copenhagen NV, Denmark.

10. Intraval Sodium: Thiopentone injection IP. May and Baker (India) Ltd., May Baker House, Bombay-25, India.

the endotracheal tube was connected to a positive phase respirator[11] for controlled ventilation. The ventilation was adjusted initially to result arterial pCO_2 between 4.66 to 5.99 kPa (35 to 45 mmHg) and arterial pO_2 essentially above 13.33 kPa (100 mmHg). The animals of other groups were allowed to respire spontaneously and endotracheal tube was connected through a three-way stop-cock to the expirograph[12]. Thus the endotracheal tube communicated with the expirograph only when respiratory minute volume was to be recorded. Normally animals ventilated air spontaneously. In these calves first recording of respiratory minute volume could be made only after initial anaesthesia and subsequent intubation. These values served as base values for further evaluation.

All the parameters were again recorded after 10 min of thiopentone anaesthesia. Subsequently repeat doses of thiopentone were administered to produce cardiopulmonary dysfunction.

Circulatory insufficiency

In animals of group I, II, III and IV only circulatory

11- Mark-14 Ventilator: Bird Corporation, Palm Springs, California-92262, U.S.A.

12- Expirograph: Advance Research Instruments Co., D-113, Guru Nanak Pura, New Delhi-18, India.

insufficiency was induced whereas ventilation was controlled. Thiopentone (5%) was administered slowly in incremental doses to cause a stable fall in mean arterial pressure (MAP). The fall of MAP to 5.6±0.21 kPa (40.87 ± 1.59 mmHg) (Mean ± Standard error) and a flat EEG (Courtin's level-7) were considered to indicate an acute thiopentone overdosage with circulatory insufficiency. All recordings were again made at this stage and following studies undertaken:

Group I - No drug was administered and calves were monitored up to 75 min. These animals served as control.

Group II - Mephentermine sulphate was given in the ear vein at the rate of 0.5 mg/kg body weight and observation made up to 60 min.

Group III - Norepinephrine bitartrate was infused in a drip through ear vein. The rate of drip was so adjusted as to maintain MAP near to that after initial anaesthesia. Once this circulatory state was achieved the rate of drip was not altered. The drip contained 2 ml of norepinephrine bitartrate solution (equivalent to 2 mg of norepinephrine base) in 500 ml of saline solution which made final concentration of the norepinephrine base as 4 µg/ml. This drip was continued for 30 min after a stable and significant rise in MAP. All parameters were monitored for another 30 min after discontinuation of the drip.

Group IV - Dexamethasone sodium phosphate was given in the ear vein slowly in incremental doses in 2.3±0.88 min at the rate of 4 mg/kg. Animals were subsequently monitored for 75 min.

Ventilatory failure

In animals of group V and VI, only ventilatory failure (Respiratory arrest) was induced by additional administration of thiopentone. Mechanical support to ventilation was not provided and animals were allowed to regain spontaneous ventilatory efforts after administration of various drugs. Soon after ventilatory failure was established, all parameters were recorded and following drugs evaluated:

Group V - Prethcamide was given into the ear vein at the rate of 9 mg/kg (0.06 ml/kg). Injection was given slowly over a period of 3.29±0.3 min. After ventilatory efforts started, observations were made for 45 min.

Group VI - Nikethamide (25%) was given in the ear vein in increments of 3 to 5 ml over a period of 6.75± 1.09 min, till the regular ventilatory efforts were established. Observations were subsequently made for 75 min.

Circulatory insufficiency and ventilatory failure

In two groups, circulatory insufficiency and ventilatory failure (Cardiopulmonary dysfunction) induced with thiopentone, was treated, only by combination of

drugs. After additional increments of thiopentone were given to produce stable hypotension and accompanied ventilatory failure, following combinations were evaluated without using any means of artificial ventilation at any stage.

Group VII - Mephentermine was given into the ear vein at the rate of 0.5 mg/kg and then prethcamide was administered at the rate of 9 mg/kg. After restoration of ventilatory efforts animals were monitored for 75 min.

Group VIII - Norepinephrine drip was started as described for group III. This was followed by nikethamide administration in incremental doses until ventilatory efforts were restored. Animals were subsequently monitored for 75 min.

Data was subjected to following statistical calculations:

Mean

Percentage

Standard error

Student's 't' test

Level of significance was seen at 5% and 1%.

All mean values were expressed with their standard error.

RESULTS

Studies were done on 40 buffalo calves divided in eight groups of five animals each. After establishing base line value (0 hr) for different parameters in all calves, thiopentone was given 'to-effect' and observations were made. These observations in all the groups, are presented under one head. The animals in six experimental groups (I, II, III, IV, VII and VIII) received additional doses of thiopentone to induce circulatory insufficiency. Whereas, group-I animals (control) were not given any other drug. The animals in other five groups received various drugs/drug combinations either to reverse ventilatory failure and/or support circulatory insufficiency. Observations made before administration of any drug or during circulatory insufficiency in these groups, are presented together under a separate heading. In the remaining two groups (V and VI) thiopentone was further administered until ventilatory failure occurred. Observations made during ventilatory failure and before administration of analeptics are also described separately. Effects of drugs, administered to support circulation and or ventilation are described separately for each drug or combination. Thus, observations of the present study are described under the following headings:

1. Thiopentone given 'to-effect'.(Groups I to VIII, n=40)
2. Thiopentone induced circulatory insufficiency and control. (Group I, II, III, IV, and VIII, n=30)
3. Thiopentone induced ventilatory failure.(Groups V and VI, n=10)
4. Mephentermine in circulatory insufficiency.(Group II)
5. Norepinephrine in circulatory insufficiency.(Group III)
6. Dexamethasone in circulatory insufficiency. (Group IV)
7. Prethamide in ventilatory failure. (Group V)
8. Nikethamide in ventilatory failure. (Group VI)
9. Mephentermine and prethamide in circulatory insufficiency with ventilatory failure. (Group VII)
10. Norepinephrine and nikethamide in circulatory insufficiency with ventilatory failure. (Group VIII)

1. Thiopentone given 'to effect'. (Groups I to VIII, n=40)

Thiopentone sodium when given 'to-effect' produced satisfactory anaesthesia and an average dose required for each animal was 9.4±0.87 mg/kg (Mean ± Standard error). There was no response from the animal to deep pin-pricks and cutaneous reflex was abolished. The calves appeared as sleeping, corneal reflex was present and palpebral reflex obtunded. Pupils were either constricted or there was downward rotation of eye balls. Jaws were relaxed, tongue flaccid, swallowing reflex abolished and endotracheal intubation could be done. Salivation was moderate to profuse. Tail was flaccid and limbs did not move even on provocation. Spontaneous ear flapping also stopped.

Electroencephalogram (EEG) had a typical complex wave form (Courtin's level-3). It had a dominance of high voltage-low frequency pattern (See figures 1-B, 7-B and 11-B).

A mild but not statistically significant, increase in heart rate (HR) and decrease in mean arterial pressure (MAP) was observed (See tables I to VIII). The heart rate values ranged between 48.8±3.1 to 59.9±2.6 min in different groups.

There was a significant ($p<0.01$) rise in central venous pressure (CVP). In all calves (n=40) values increased from 1.24±0.172 to 2.08±0.211 kPa (12.68±1.95 to 20.68±0.97 cmH_2O). This rise in CVP was consistent in all groups irrespective of controlled positive pressure ventilation.

The electrocardiogram of one calf from group VII showed II-degree AV-block type II. Primary T-wave and or ST-segment changes were observed in 22 calves (Increased amplitude-16; biphasic T-wave-3; change in polarity-3; ST-segment elevation-2 and ST-segment depression-9). II-degree AV-block observed in 0 hr tracings (i.e. before administration of the thiopentone) in three calves was abolished after thiopentone administration and did not show any complication regarding this during further course of the experiment.

In spontaneously breathing calves (Groups-V, VI, VII and VIII) there were no marked changes in the respiratory

rate. In calves where ventilation was controlled (Groups I, II, III and IV) the arterial pCO_2 remained within the normal range of 0 hr values, and the pO_2 markedly increased and remained always above 13.3 kPa (100 mmH_g). But in spontaneously breathing calves mild to moderate increase in pCO_2 and significant decrease ($p<0.05$ or $p<0.01$) in pO_2 was observed. Venous oxygen tension had a tendency to increase, during controlled ventilation, while in spontaneously breathing calves it had a decreasing trend.

Respiratory minute volume (Groups V, VI, VII and VIII) could be recorded only after intubation and the average value in these 20 animals was 6.353 ± 1.081 l/min.

Rectal temperature, blood haemoglobin, plasma total proteins and plasma creatinine were not affected. Blood glucose levels had a tendency towards increase in all the groups (See tables I to VIII).

2. Thiopentone induced circulatory insufficiency and control. (Groups I, II, III, IV, VII and VIII). n=30).

These 30 animals from groups I, II, III, IV, VII and VIII had received 9.7 ± 1.13 mg/kg of thiopentone for routine anaesthesia and additional 14.3 ± 2.35 mg/kg (147.42%) of thiopentone in increments was required to produce a stable hypotension. There was a 69.3% fall in MAP i.e. decrease from 0 hr values of 17.75 ± 0.748 kPa (133.1 ± 5.61 mmHg) to 5.45 ± 0.211 kPa (40.9 ± 1.59 mmHg).

The decrease was both in systolic as well as in diastolic pressures.

All the calves were deeply anaesthetised. Corneal and palpebral reflexes were abolished and eyes were open. Pupils initially remained constricted but were dilated in due course of time. Capillary refill time (blanching of tongue) was increased. In initial stages of this profound hypotension, ECG revealed Courtin's level-5 & 6 (Fig.1). The periodic electrical silence in ECG was separated by irregular high voltage complexes. This electrical silence varied between 3 to 10 s and subsequently there was a complete electrical silence (Courtin's level-7).

During this circulatory insufficiency, there was slight increase in HR from 44.6±4.06 to 57.8±4.14/min (n=30) but was not statistically significant. Central venous pressure was markedly ($p<0.01$) increased. Zero hour values (n=30) of 1.24±0.196 kPa (12.67±2.01 cmH_2O) were raised to 3.86±0.339 kPa (39.33±3.451 cmH_2O).

In the ECG, primary T-wave changes and ST-segment elevation or depression were seen in 25 calves. Only one calf from group II, developed III-degree AV-block. Animal No.82MRO3 from group-VII had II-degree AV-block before induction of circulatory insufficiency and it continued during this period also.

In the calves from groups I, II, III and IV ventilation was artificially controlled and blood gases

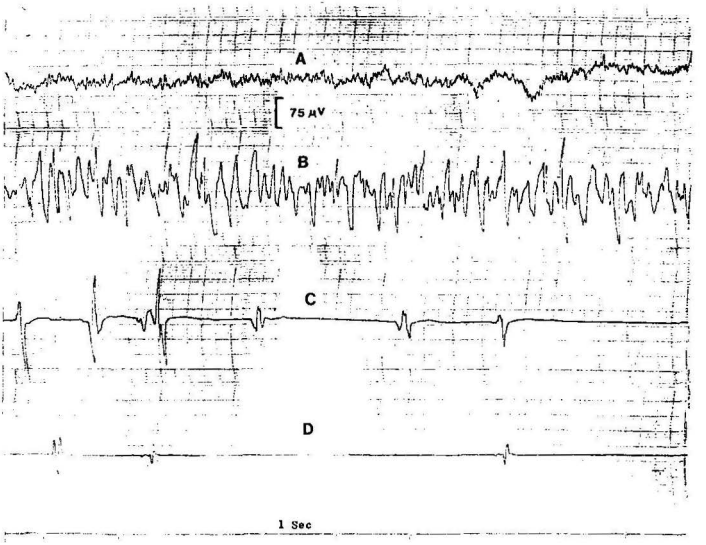

Fig. 1. Showing EEG changes during thiopentone induced circulatory insufficiency.

A = Tracing obtained before administration of thiopentone (0 hr). Showing low voltage-high frequency pattern.

B = After thiopentone given 'to-effect' i.e. routine anaesthesia. Showing typical complex wave form (Courtin's level-3).

C & D = After excessive doses of thiopentone, to induce circulatory insufficiency. Showing loss of electrical activity in progress (Courtin's level-5 & 6).

were within predictable range. In calves from groups VII and VIII ventilatory support was not provided during circulatory insufficiency accompanied by ventilatory failure. There was a marked ($p<0.01$) increase in the arterial pCO_2 and decrease ($p<0.05$) in both arterial and venous oxygen tensions.

Rectal temperature, blood haemoglobin, plasma total proteins and plasma creatinine were not affected. Blood glucose had an increasing trend when compared with 0 hr values. Increase was statistically significant ($p<0.05$) in calves from groups VII and VIII where ventilatory failure also coexisted.

Group-I (Control)

In the animals of group-I after inducing circulatory insufficiency with further administration of thiopentone, no treatment was given except monitored for 75 min. One calf died by 15 min and other two died when respirator was weaned.

Out of four calves only two had evidence of electrical activity in ECG (Courtin's level-5 and 6) by 60 and 75 min. Pupils were constricted and corneal reflex was mild by then. Cutaneous reflex did not return in any calf. When at termination of the experiment (i.e. after 75 min) respirator was weaned, two calves had weak respiratory efforts and in other two respiratory efforts were not initiated and died consequently.

Induction of hypotension with the additional doses of thiopentone in these animals caused a moderate increase ($p<0.05$) in HR which subsequently reached near 0 hr values by 15 min. The severe fall in systolic, diastolic and mean arterial pressure showed some improvement by 30 min, but values were always lower ($p<0.01$) than 0 hr values. In initial stages of circulatory insufficiency, there was a marked increase in CVP and after 15 min it decreased considerably ($p<0.05$; $p<0.01$) but values remained always significantly higher ($p<0.05$) than 0 hr values.

The arterial pCO_2 remained within normal range for an hour but afterwards it increased ($p<0.05$). Venous oxygen tensions remained relatively low.

There were no significant changes in rectal temperature, blood haemoglobin, plasma total proteins, plasma creatinine and blood glucose. However, in later stages, blood glucose had a tendency to decrease.

Data of all parameters is given in table I. One calf (No.63NHCO2) died 15 min after circulatory insufficiency was induced. The ECG remained always flat. Mean arterial pressure further decreased from induced hypotensive value of 5.99 kPa (45 mmHg) to 3.55 kPa (26.66 mmHg) and CVP further increased from 4.42 kPa (45 cmH_2O) to 4.91 kPa (50 cmH_2O). Arterial pO_2 was above normal but venous pO_2 decreased to 2.19 kPa (16.4 mmHg). Electrocardiogram depicted HR of 68/min with normal QRS complex and with

Table I: The effects of thiopentone sodium induced circulatory insufficiency in buffalo calves (Group-I).

Parameter (units)	0 hour	Thiopentone administration: 10 min after anaesthesia	Thiopentone administration: Induced circulatory insufficiency	Minutes after induced circulatory insufficiency: 15	30	45	60	75
	n=5	n=5	n=5	n=5	n=4	n=4	n=4	n=4
Heart rate (per min)	42.6 (3.56)	49.5 (4.45)	54.2[a] (0.66)	44.8[y] (4.42)	47.7[y] (2.28)	47.3 (4.43)	50.3 (6.86)	53.4 (7.65)
Mean arterial pressure (kPa)	18.66 (0.670)	17.11 (0.708)	5.11[b] (0.222)	5.86[b] (0.536)	8.77[by] (0.728)	8.88[by] (0.933)	9.47[bz] (0.571)	9.89[bz] (0.692)
Systolic pressure (kPa)	20.88 (0.728)	18.88 (0.831)	6.44[b] (0.192)	6.89[b] (0.619)	10.99[bz] (0.695)	10.66[by] (0.855)	11.33[by] (0.564)	11.66[by] (0.832)
Diastolic pressure (kPa)	17.55 (0.618)	16.22 (0.694)	4.44[b] (0.192)	5.33[b] (0.553)	7.66[by] (0.399)	7.99[bz] (0.588)	8.66[bz] (0.653)	8.99[bz] (0.604)
Central venous pressure (kPa)	1.29 (0.162)	2.09 (0.270)	4.74[b] (0.239)	2.94[ay] (0.330)	2.80[az] (0.242)	2.84[bz] (0.208)	2.99[ay] (0.312)	3.06[ay] (0.384)
Arterial carbon dioxide tension (kPa)	4.91 (0.186)	4.27 (0.309)	4.26 (0.327)	5.06 (0.505)	5.25 (0.455)	5.76 (0.324)	6.30[y] (0.390)	6.32[ay] (0.391)
Arterial oxygen tension (kPa)	10.20 (0.227)	17.66[b] (1.466)	14.90[a] (1.548)	16.18[b] (0.970)	14.97[b] (0.970)	14.65[a] (1.151)	14.58[a] (1.098)	15.57[a] (1.272)
Venous oxygen tension (kPa)	5.25 (0.268)	6.07 (0.432)	5.36 (0.459)	4.33[b] (0.075)	4.35 (0.262)	4.18[a] (0.161)	3.91[az] (0.385)	4.35 (0.392)
Rectal temperature (°C)	37.6 (0.06)	37.3 (0.12)	37.3 (0.17)	36.6 (0.08)	36.6 (0.09)	36.5 (0.10)	36.2 (0.16)	36.1 (0.24)
Blood glucose (mmol/l)	4.58 (0.166)	5.11 (0.237)	5.23 (0.315)	4.99 (0.160)	4.77 (0.194)	4.73 (0.164)	4.61[y] (0.299)	3.51[y] (0.481)
Haemoglobin (g/l)	118.0 (9.85)	116.5 (10.53)	115.3 (9.29)	119.5 (9.21)	121.5 (9.23)	122.0 (9.27)	122.5 (9.27)	121.6 (9.58)
Plasma total proteins (g/l)	75.5 (1.73)	75.2 (1.88)	73.0 (1.95)	74.0 (1.42)	73.9 (1.82)	74.2 (2.01)	74.1 (1.49)	73.9 (1.83)
Plasma creatinine (μ mol/l)	186 (10.6)	172 (13.3)	181 (4.4)	163 (13.3)	176 (4.6)	177 (7.3)	185 (6.8)	186 (8.7)

Figures in parentheses indicate standard error of the mean. n = Number of animals.

a= $p < 0.05$; b= $p < 0.01$ - Compared with 0 hour value.

y= $p < 0.05$; z= $p < 0.01$ - Compared with induced circulatory insufficiency value.

time there was a progressive decrease in HR and QRS amplitude until an isoelectric line was seen on ECG monitor.

3. Thiopentone induced ventilatory failure.(Groups V and VI, N=10).

This was done in two groups (V and VI) and analeptics were evaluated. Anaesthesia in these 10 calves was induced with 9.0±1.1 mg/kg of thiopentone and a further increment of 12.8±2.0 mg/kg (140%) was required to produce ventilatory failure. There was complete cessation of ventilatory movements, and no evidence of ingress and egress of air through the endotracheal tube. All calves appeared to be more deeply anaesthetised. In initial stages of ventilatory failure, corneal and palpebral reflexes were moderately depressed, eye lids closed and pupils constricted. But as the time elapsed (collection of samples, making recordings before administration of analeptics) depression was more severe. In four calves, corneal reflex was abolished and in three calves, pupils became dilated. The EEG revealed all levels of Courtin's between 3 and 7. In initial stages of ventilatory failure, it was like Courtin's level-3 i.e. complex wave form, but as the time of complete ventilatory failure advanced, EEG started showing periods of electrical silence (See figure 7 C and D).

During the ventilatory failure in these 10 calves marked changes occurred in the cardiovascular parameters. When compared with base values, HR increased from 46.8 to 52.4/min

and MAP decreased from 17.33 kPa (123 mmHg) to 6.66 kPa (49.8 mmHg). This was then followed by an increase in MAP to 16.33 kPa (122.6 mmHg) with the HR of 85.6/min. During this tachycardia two animals had junctional rhythm and one did exhibit occasional ventricular beats too. There always remained a marked increase in CVP.

As expected, arterial CO_2 tension increased significantly ($p<0.01$) and both arterial and venous O_2 tension decreased considerably ($p<0.01$).

Rectal temperature, blood haemoglobin, plasma total proteins and plasma creatinine did not exhibit any change in their levels, however, blood glucose was significantly increased ($p<0.05$) in both the groups.

4. Mephentermine in circulatory insufficiency. (Group II)

After mephentermine administration at the rate of 0.5 mg/kg, i.v., restoration of corneal and palpebral reflexes began within 15 min and always followed the return of pupillary reflex (constriction of pupils).

Electrical activity in the ECG was noticed 2.47±0.32 min after the mephentermine administration (Fig.2). The ECG wave patterns were either delta, or delta and theta rhythm and later on a complex wave form was observed.

Cardiovascular action of the mephentermine started 1.16±0.24 min after its administration and by 1.99±0.38 it had its peak effect which was characterised by rise in arterial pressure above 0 hr values. After an over-

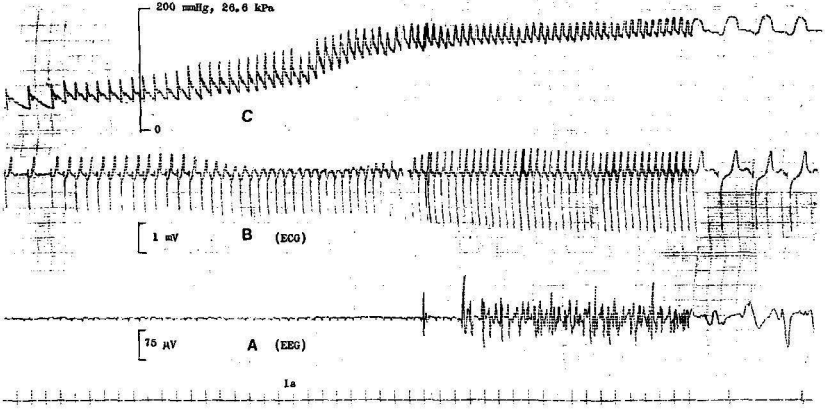

Fig. 2. A typical response to mephentermine administration in a buffalo calf with *thiopentone induced circulatory* insufficiency.

A = Returning electrical activity in EEG.

B = Tachycardia and primary T-wave changes.

C= Rising arterial pressure.

(Tracing starts from 50s after mephentermine administration.)

shooting of arterial pressure (systolic, diastolic and mean), 0 hr values were resumed within 5 min and remained in the normal range thereafter, throughout the period of observation. There was a marked increase ($p<0.01$) in the HR for 15 min and thereafter it returned towards normalcy. Highly elevated CVP recorded during induced circulatory insufficiency, decreased considerably ($p<0.01$) following mephentermine administration. The fall in CVP was more than 0 hr values up to 15 min ($p<0.05$) and thereafter remained in normal range (Table-II).

The animal No.37MC8, which had developed III-degree AV-block during induced circulatory insufficiency was ameliorated by mephentermine administration (Fig.3). This calf did not exhibit any arrhythmia subsequently. Occasional junctional and ventricular pacing was observed in another calf at 15 min after mephentermine administration. In calf No.36MC5, soon after administration of the mephentermine, when arterial pressure started rising, ectopic beats for a brief period were observed and subsequently sinus rhythm was established. The most frequent ECG changes were of T-wave and ST-segment.

Arterial oxygen tension remained elevated, throughout the period of study while venous oxygen and arterial carbon dioxide tensions remained within normal limits (See table II).

There were no significant changes in blood haemoglobin, plasma total proteins and plasma creatinine. Mild degrease

Table II: The effects of mephentermine sulphate @ 5 mg/kg i.v. following thiopentone sodium induced circulatory insufficiency in buffalo calves (Group-II).

Parameter (units)	0 hour	Thiopentone administration		Minutes after mephentermine administration					
		10 min after anaesthesia	Induced circulatory insufficiency	5	10	15	30	45	60
	n=5	n=5	n=5	n=5	n=5	n=5	n=5	n=5	n=5
Heart rate (per min)	41.8 (5.12)	57.3 (7.21)	58.0 (8.12)	108.4^{by} (8.61)	107.8^{by} (8.16)	90.4^{by} (4.78)	57.4 (3.83)	46.5 (6.65)	44.8 (6.32)
Mean arterial pressure (kPa)	21.50 (0.671)	20.28 (0.554)	5.99^{b} (0.794)	21.06^{z} (1.191)	20.88^{z} (0.777)	20.08^{z} (0.869)	18.30^{z} (1.043)	17.95^{z} (1.078)	18.02^{z} (1.116)
Systolic pressure (kPa)	24.26 (0.487)	22.33^{a} (0.471)	8.53^{b} (0.779)	22.92^{z} (0.866)	22.39^{z} (0.730)	21.59^{az} (0.811)	19.99^{az} (0.837)	19.19^{az} (0.908)	19.21^{az} (0.804)
Diastolic pressure (kPa)	20.13 (0.455)	19.26 (0.522)	5.06^{b} (0.657)	20.13^{z} (0.999)	20.13^{z} (0.656)	19.33^{z} (0.656)	17.46^{z} (1.015)	17.33^{az} (0.887)	17.43^{az} (1.001)
Central venous pressure (kPa)	1.16 (0.131)	1.71 (0.227)	3.26^{b} (0.314)	0.47^{az} (0.127)	0.61^{az} (0.095)	0.76^{az} (0.027)	1.18^{y} (0.315)	1.52^{y} (0.243)	1.52^{y} (0.220)
Arterial carbon dioxide tension (kPa)	4.88 (0.281)	5.29 (0.236)	5.05 (0.270)	-	-	5.45 (0.371)	5.38 (0.166)	5.03 (0.146)	5.09 (0.176)
Arterial oxygen tension (kPa)	9.98 (0.264)	20.17^{b} (1.375)	18.60^{b} (1.667)	-	-	20.10^{b} (1.145)	20.36^{b} (1.289)	21.89^{b} (1.535)	22.53^{b} (1.402)
Venous oxygen tension (kPa)	5.43 (0.245)	6.06 (1.137)	5.84 (0.369)	-	-	6.32 (0.389)	6.26 (0.325)	5.77 (0.321)	6.04 (0.295)
Rectal temperature (°C)	37.9 (0.27)	37.7 (0.29)	37.2 (0.24)	-	-	36.9 (0.25)	36.8 (0.41)	36.8^{a} (0.28)	36.7^{a} (0.29)
Blood glucose (mmol/l)	4.13 (0.115)	5.02 (0.521)	6.08 (0.48)	-	-	6.27^{a} (0.497)	5.31^{a} (0.375)	4.86 (0.386)	4.88 (0.388)
Haemoglobin (g/l)	132.2 (6.25)	128.0 (6.56)	115.3 (7.50)	-	-	125.2 (3.44)	123.6 (1.12)	126.2 (3.21)	125.4 (2.30)
Plasma total proteins (g/l)	75.80 (1.26)	74.60 (1.42)	73.00 (1.52)	-	-	73.80 (1.62)	72.50 (1.63)	72.90 (0.42)	73.00 (1.11)
Plasma creatinine (µ mol/l)	177 (9.5)	176 (10.2)	183 (11.7)	-	-	162 (11.3)	159 (11.8)	163 (9.4)	169 (7.69)

Figures in parentheses indicate standard error of the mean. n = Number of animals.

a = $p < 0.05$; b = $p < 0.01$ - Compared with 0 hour value.

y = $p < 0.05$; z = $p < 0.01$ - Compared with induced circulatory insufficiency value obtained before administration of mephentermine.

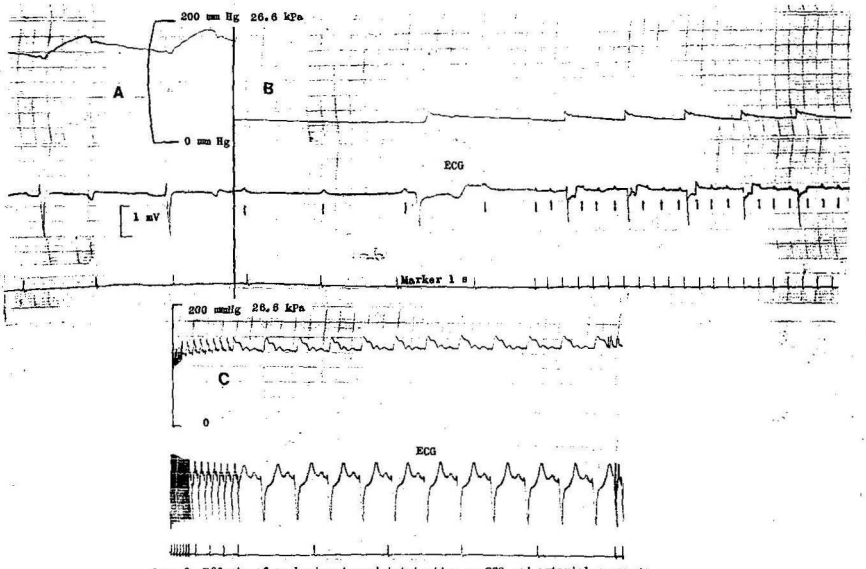

Fig. 3. *Effects* of mephentermine administration on ECG and arterial pressure in an animal No 37M03.

A = 0 hr tracing of ECG, showing heart rate of 35/min, and arterial pressure of 21.3/12 3 kPa (Systolic/Diastolic).

B = Tracing obtained during thiopentone induced circulatory insufficiency. ECG showind IIIrd degree AV-block with ventricular rate of 16/min. Upper tracing shows arterial pressure 8.0/3.3 kPa.

C = Tracing soon after mephentermine administration. ECG showing abolishing of AV-block and tachycardia. ST-segment depression and primary T-wave changes are seen. Upper tracing shows rising arterial pressure to 23.3/20.0 kPa.

in rectal temperature was observed in later stages of the experiment. Moderately elevated blood glucose levels during circulatory insufficiency was further elevated by nephentermine administration (See table-II).

5. Norepinephrine in circulatory insufficiency (Group-III)

When circulatory insufficiency, characterised by hypotension (MAP= 5.22±0.816 kPa or 39.2±6.12 mmHg), was induced with thiopentone, a saline drip containing 4 µg/ml of norepinephrine base was started. The rate of drip was so adjusted as to get a near normal MAP, but essentially lower than the 0 hr values. Drip continued at this rate for 30 min. Total aliquot given in 30 min, was 113.5±21.65 ml or 5.8±.084 µg of NE base/kg or 0.19±0.01 µg of NE base/kg/min.

Corneal and palpebral reflexes started returning by 45 to 60 min after start of the infusion, and as in calves of group-II their return was always preceeded by constriction of the dilated pupils. Electrical activity in the ECG returned within 1.63±0.18 min after start of the drip. The wave forms in the ECG were mixed. In initial stages (15-30 min), high voltage-low frequency pattern was superimposed by low voltage-high frequency waves.

Cardiovascular action of the norepinephrine drip started 1.19±0.28 min after its initiation and near normal range of the arterial pressure could be achieved by 4.81±0.84 min. Heart rate did not show any significant alterations. Arterial pressure was within 0 hr value range by 5 min.

A careful perusal of the data revealed that, after start of the drip, there was a progressive increase in arterial pressure until 0 hr limits were achieved (it may be noted that once the rate of the drip was set at initial stages, it was not altered for 30 min). When the drip was disconnected arterial pressure had a tendency to fall but values were within 0 hr limits. The elevated CVP, recorded during circulatory insufficiency also decreased ($p<0.05$) after start of the norepinephrine drip but effect was slow, as values remained significantly elevated ($p<0.05$) than 0 hr values up to 15 min. Disconnection of the drip did not affect the trend in CVP (Table-III).

Besides primary T-wave changes, ECG studies revealed occasional hypodynamic premature nodal beats, throughout the period of observation in one animal (Fig.4). In other calf (42NE03), isorhythmic dissociation developed after the drip was disconnected and remained throughout thereafter (Fig.5). In another calf, ectopic and effective beats were observed 15 min after start of the norepinephrine drip and remained for 30 min.

Arterial and venous oxygen tension and arterial carbon-dioxide tension values did not show any difference in trend from the calves of group-II, as ventilation was controlled. Rectal temperature, blood glucose, blood haemoglobin, plasma total proteins and plasma creatinine were not affected (See table-III).

Table III: The effects of norepinephrine drip (4 µg/ml) following thiopentone sodium induced circulatory insufficiency in buffalo calves (Group-III).

Parameter (units)	0 hour	Thiopentone administration		Minutes after start of norepinephrine				Minutes after disconnecting drip	
		10 min after anaesthesia	Induced circulatory insufficiency	5	10	15	30	15	30
	n=5	n=5	n=5	n=5	n=5	n=5	n=5	n=5	n=5
Heart rate (per min)	43.2 (5.71)	45.6 (3.85)	55.1 (4.23)	53.9 (3.23)	52.8 (2.93)	56.6 (2.43)	55.1 (2.59)	56.2 (4.14)	57.9 (4.50)
Mean arterial pressure (kPa)	17.55 (0.394)	17.16 (0.597)	5.22^{b} (0.816)	15.27^{z} (0.853)	16.94^{z} (0.921)	18.27^{z} (0.685)	18.39^{z} (0.539)	17.49^{z} (0.789)	16.11^{z} (0.675)
Systolic pressure (kPa)	20.33 (0.577)	19.49 (0.738)	7.66^{b} (1.005)	17.50^{z} (0.699)	18.83^{z} (0.857)	20.16^{z} (0.667)	20.16^{z} (0.554)	19.16^{z} (0.699)	17.99^{z} (0.773)
Diastolic pressure (kPa)	16.16 (0.319)	15.99 (0.544)	3.99^{b} (0.769)	14.16^{z} (0.887)	15.99^{z} (1.053)	17.33^{z} (0.719)	17.49^{z} (0.499)	16.66^{z} (0.847)	15.16^{z} (0.757)
Central venous pressure (kPa)	1.10 (0.209)	2.11^{a} (0.231)	3.43^{b} (0.495)	-	-	2.04^{a,y} (0.197)	1.84^{y} (0.264)	1.69^{y} (0.338)	1.58^{y} (0.267)
Arterial carbon dioxide tension (kPa)	5.55 (0.298)	4.64 (0.351)	4.79 (0.379)	-	-	5.38 (0.407)	4.86 (0.364)	4.43 (0.414)	4.67 (0.320)
Arterial oxygen tension (kPa)	10.46 (0.357)	23.98^{b} (2.095)	22.48^{b} (2.193)	-	-	28.76^{b} (2.736)	26.96^{b} (2.645)	26.66^{b} (2.702)	29.39^{b} (3.435)
Venous oxygen tension (kPa)	6.01 (0.237)	6.69 (0.825)	6.08 (0.305)	-	-	6.71 (0.479)	6.74 (0.656)	6.36 (0.408)	6.13 (0.504)
Rectal temperature (°C)	37.8 (0.33)	37.7 (0.27)	37.6 (0.35)	-	-	37.1 (0.38)	37.1 (0.47)	36.7 (0.51)	36.6 (0.49)
Blood glucose (mmol/l)	4.59 (0.135)	5.29 (0.386)	4.94 (0.387)	-	-	4.79 (0.168)	4.80 (0.439)	4.96 (0.252)	3.92 (0.252)
Haemoglobin (g/l)	118.7 (5.67)	119.7 (3.76)	118.3 (2.33)	-	-	118.7 (2.97)	115.0 (3.21)	114.6 (3.18)	117.3 (4.26)
Plasma total proteins (g/l)	77.00 (1.64)	76.50 (1.24)	74.90 (1.92)	-	-	76.00 (1.71)	75.00 (1.01)	76.50 (1.91)	77.00 (1.94)
Plasma creatinine (µ mol/l)	166 (16.8)	148 (13.5)	170 (11.58)	-	-	174 (15.1)	166 (9.7)	162 (27.5)	161 (16.8)

Figures in parentheses indicate standard error of the mean. n = Number of animals.

a = $p < 0.05$; b = $p < 0.01$ - Compared with 0 hour value.

y = $p < 0.05$; z = $p < 0.01$ - Compared with induced circulatory insufficiency value obtained before starting norepinephrine drip.

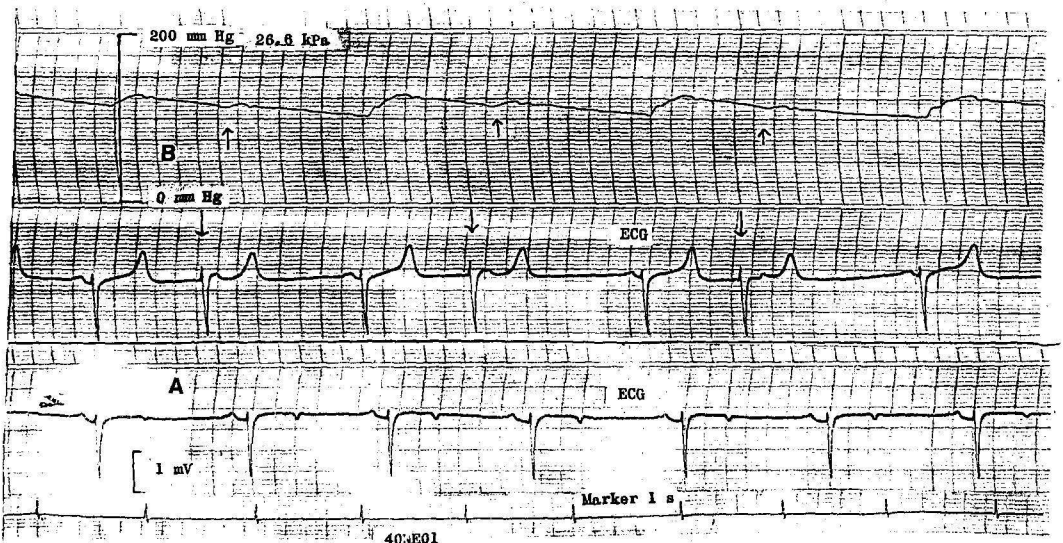

Fig. 4.

A = Normal (0 hr) ECG tracing showing heart rate of 42/min.

B = A 30 *min* tracing of simultaneous ECG and arterial pressure. Arrow indicates hypodynamic premature nodal beats. Note heart rate of 48/min and primary T-wave changes.

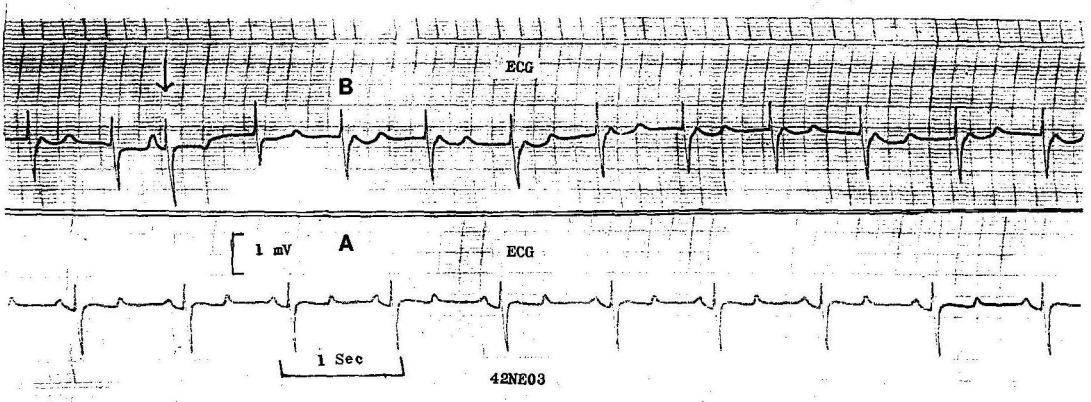

Fig. 5. Showing isorhythmic dissociation after norepinephrine administration.

A = Normal (0hr) tracing.

B = Tracing obtained 15 min after disconnecting norepinephrine drip. Showing isorhythmic dissociation. Arrow indicates a captured beat.

6. Dexamethasone in circulatory insufficiency. (Group IV)

Further administration of thiopentone in these calves caused a fall in MAP from 16.77±0.712 kPa (125.8±5.34 mmHg) to 4.89±0.433 kPa (36.3±3.25 mmHg), which suggested circulatory insufficiency. Dexamethasone sodium phosphate was then given slowly into the ear vein at the rate of 4 mg/kg. Dilated pupils were constricted within 15 min after dexamethasone administration and by 30 to 45 min resumption of corneal and palpebral reflex activity started. In two calves weak respiratory efforts started after 60 min, but controlled ventilation was continued until experiment was terminated.

Electrical activity in the EEG began to appear between 40s and 5 min but were essentially after there was an appreciable increase in MAP. Wave configuration was almost similar to that observed in calves of group-III.

The arterial pressure began rising 1.75±0.76 min after dexamethasone administration and values were more stable by 3.19±0.77 min. There was a considerable increase in arterial pressure and statistically values were near 0 hr values by 45 min. There were no significant changes in the heart rate. Although dexamethasone significantly lowered the elevated CVP but remained higher ($p<0.05$) than 0 hr values, until 45 min (Table-IV).

Animal No.74404 showed undulatory changes in arterial pressure in initial stages, without major changes in ECG.

Table IV: The effects of dexamethasone-sodium-phosphate @ 4 mg/kg i.v. following thiopentone sodium induced circulatory insufficiency in buffalo calves (Group-IV).

Parameter (units)	0 hour	Thiopentone administration		Minutes after dexamethasone administration					
		10 min after anaesthesia	Induced circulatory insufficiency	5	15	30	45	60	75
	n=5	n=5	n=5	n=5	n=5	n=5	n=5	n=5	n=5
Heart rate (per min)	50.8 (4.91)	62.9 (5.08)	65.4 (5.33)	67.8 (5.47)	73.4 (8.34)	73.1 (8.95)	63.8 (4.75)	52.4 (4.21)	52.5 (4.32)
Mean arterial pressure (kPa)	16.99 (0.534)	16.78 (0.712)	4.69^{b} (0.433)	14.33^{az} (0.707)	13.167^{az} (1.086)	13.94^{az} (1.023)	14.11^{z} (0.999)	15.85^{z} (0.945)	15.86^{z} (0.948)
Systolic pressure (kPa)	18.99 (0.638)	17.66 (0.748)	6.03^{b} (0.868)	15.67^{az} (0.897)	14.83^{az} (1.131)	15.49^{az} (1.043)	15.67^{az} (1.045)	17.33^{z} (1.068)	17.35^{z} (1.15)
Diastolic pressure (kPa)	15.99 (0.461)	16.17 (0.785)	4.03^{b} (0.687)	13.67^{z} (0.609)	12.33^{az} (0.686)	13.17^{az} (0.752)	13.33^{az} (0.840)	15.11^{z} (1.018)	15.12^{z} (0.962)
Central venous pressure (kPa)	1.42 (0.131)	2.50^{a} (0.193)	4.49^{b} (0.191)	-	2.33^{az} (0.216)	2.01^{z} (0.196)	2.06^{az} (0.172)	1.99^{z} (0.199)	1.94^{z} (0.192)
Arterial carbon dioxide tension (kPa)	4.79 (0.264)	4.88 (0.295)	5.11 (0.338)	-	5.32 (0.383)	5.21 (0.294)	5.27 (0.330)	4.92 (0.387)	4.86 (0.323)
Arterial oxygen tension (kPa)	11.54 (0.301)	17.94^{b} (1.392)	16.33^{b} (1.588)	-	17.38^{b} (1.392)	16.17^{b} (0.941)	17.45^{b} (1.358)	17.79^{b} (1.031)	19.11^{b} (1.592)
Venous oxygen tension (kPa)	4.92 (0.225)	5.68 (0.627)	4.02 (0.186)	-	4.83 (0.485)	5.12 (0.515)	5.29 (0.566)	5.52 (0.557)	5.07 (0.454)
Rectal temperature (^{o}C)	37.8 (0.16)	37.6 (0.19)	37.5 (0.16)	-	37.3 (0.25)	37.1^{a} (0.14)	37.2^{a} (0.11)	37.3^{a} (0.11)	37.3 (0.25)
Blood glucose (mmol/l)	3.97 (0.222)	4.47 (0.188)	4.44 (0.275)	-	5.30^{a} (0.344)	5.04^{a} (0.294)	5.13^{a} (0.267)	5.03 (0.385)	4.19 (0.289)
Haemoglobin (g/l)	116.0 (7.12)	119.2 (4.94)	115.7 (6.0)	-	115.6 (5.27)	112.0 (6.77)	105.7 (7.06)	112.7 (4.90)	115.5 (7.53)
Plasma total proteins (g/l)	75.80 (1.71)	74.50 (0.96)	70.00 (1.31)	-	74.50 (0.50)	74.00 (0.82)	73.50 (1.50)	74.50 (1.89)	73.50 (1.50)
Plasma creatinine (μ mol/l)	108 (17.1)	111 (11.7)	112 (15.9)	-	119 (15.5)	124 (9.9)	117 (14.2)	130 (10.1)	106 (6.2)

Figures in parentheses indicate standard error of the mean. n = Number of animals.

a = $p < 0.5$; b = $p < 0.01$-Compared with 0 hour value.

y = $p < 0.05$; z = $p < 0.01$ - Compared with induced circulatory insufficiency value obtained before dexamethasone administration.

Three calves showed primary T-wave changes and ST-segment depression throughout the period of study.

Animal No.71001 developed ventricular tachycardia 20 min after dexamethasone administration followed by ventricular flutter with a fall in MAP from 11.11 kPa (83.3 mmHg) to 7.78 kPa (58.3 mmHg). This flutter remained for 20 min and spontaneously resumed to ventricular tachycardia with rise in MAP to 11.11 kPa (83.3 mmHg). Within 10 min later, sinus rhythm was established and animal survived (Fig.6).

The trend in arterial pO_2, pCO_2 and venous pO_2 after dexamethasone administration was similar to that of calves of group II and III (See table-IV).

There was a slight fall in rectal temperature. Blood haemoglobin, plasma total proteins and plasma creatinine were not affected. Dexamethasone caused a significant increase in the blood glucose for 45 min. (See table-III).

7. Prothamide in ventilatory failure. (Group V)

In this group of five animals ventilatory failure was induced with additional increments of thiopentone and no mechanical support was provided. Instead, prothamide 9 mg/kg was given slowly into the ear vein. Animals made efforts of respiration by 2.6±0.47 min after its administration. Within 5 min corneal and palpebral reflexes returned. Cutaneous reflex was also present and

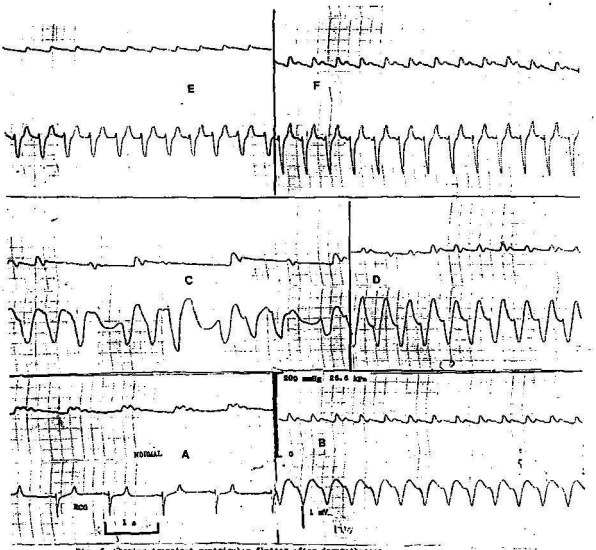

Fig. 5. Showing transient ventricular flutter after desmethoxene administration in an animal with thiopentone induced circulatory insufficiency.

A - Normal (0 hr) tracing showing heart rate (HR) of 58/min, systolic and diastolic arterial pressure of 17.3/14.7 kPa with mean arterial pressure (MAP) of 16.0 kPa (117 mmHg).

B - Tracing obtained 30 min after desmethoxene administration. Showing ventricular tachycardia; HR 130/min & MAP 11.1 kPa.

C - 35 min tracing. Showing ventricular flutter and MAP 7.8 kPa.

D - 45 min tracing. Resumption of ventricular tachycardia with HR 150/min and MAP 11.1 kPa.

E - 50 min tracing. Showing ventricular tachycardia with decreasing HR to 130/min and increasing MAP to 16.7 kPa.

F - 60 min tracing. Finally establishing sinus rhythm (Sinus tachycardia) with HR 130/min and MAP 12.4 kPa.

there was frequent but unprovoked flapping of ears by 15 min. Rapid volley of deep pin-pricks stimulated the animals, eyes appeared wide awake with pupils dilated.

In one animal, greater excitement was observed after 8 min of the prethenamide administration. In this calf, pin-pricks initiated movements of the limbs, ear flapping, muscle twitching, movement of jaws and struggling for endotracheal tube.

Electrical activity in the EEG started by 1.5±0.25 min after prethenamide administration. High voltage-high frequency patterns in EEG remained for 30-45 min. Resumption of electrical activity began with irregular bursts of high voltage waves, and with time the interval between the bursts decreased. Subsequently this pattern rapidly shifted to complex wave form and finally stabilised to high voltage-high frequency pattern (Fig.7).

The respirations were jerky for initial 5 to 10 min and then became regular. Respiratory rate remained higher ($p<0.05$) throughout the period of study. Respiratory minute volume was relatively higher than the values obtained during routine anaesthesia (after thiopentone anaesthesia with spontaneous ventilation) and remained significantly higher ($p<0.01$) at 15 and 30 min interval. Marked decrease ($p<0.01$) in the blood oxygen tension and rise ($p<0.01$) in the carbon dioxide tension recorded during the ventilatory failure was ameliorated ($p<0.05$; $p<0.01$) by the prethenamide administration, within 15 min (Table-V).

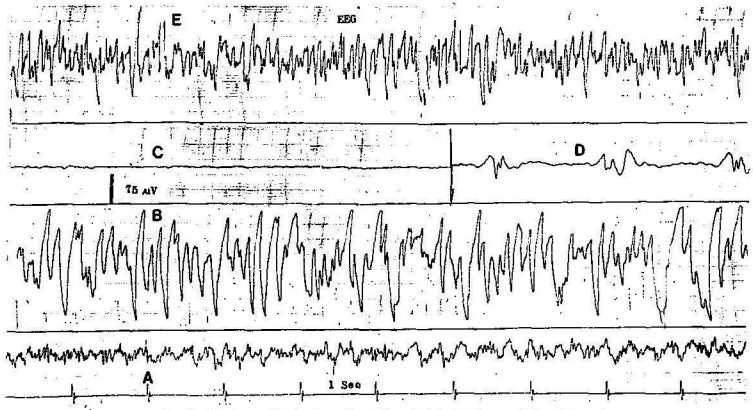

Fig. 7. Showing effect of prethcamide administration on EEG pattern in buffalo calves deeply anaesthetised with thiopentone.

A = Tracing obtained before administration of thiopentone (0 hr). Showing low voltage-high frequency pattern.

B = After thiopentone given 'to-effect' and animal breathing spontaneously. Showing typical complex wave form (Courtin's level-3)

C = Tracing obtained during later stage of ventilatory failure, induced by additional administration of thiopentone. Showing complete electrical silence (Courtin's level-7)

D = Tracing obtained 95 s after prethcamide administration. Showing resumption of electrical activity (Courtin's level-4)

E = A 15 min tracing showing high voltage-high frequency pattern.

Table V: The effects of prethcamide @ 9 mg/kg i.v. following thiopentone sodium induced ventilatory failure in buffalo calves (Group-V).

Parameter (units)	0 hour	Thiopentone administration			Minutes after prethcamide administration			
		10 min after anaesthesia	Induced ventilatory failure I	Induced ventilatory failure II	5	15	30	45
	n=5	n=5	n=5	n=5	n=5	n=5	n=5	n=5
Heart rate (per min)	48.4 (4.52)	54.7 (2.09)	54.3 (2.74)	72.5[a] (7.25)	57.0[y] (2.75)	73.0[a] (8.25)	64.8 (5.91)	58.1[y] (4.30)
Mean arterial pressure (kPa)	17.44 (0.616)	16.05 (0.718)	6.89[b] (0.992)	15.66 (0.692)	12.88[a] (0.923)	14.74[a] (0.726)	15.99 (1.066)	16.37 (0.612)
Systolic pressure (kPa)	18.66 (0.636)	17.16 (0.576)	8.66[b] (1.342)	18.66 (1.282)	15.99[a] (0.674)	17.65 (0.561)	18.36 (1.187)	18.44 (0.694)
Diastolic pressure (kPa)	16.33 (0.439)	13.99 (1.021)	5.99[b] (0.993)	14.16 (0.826)	11.33[b] (0.722)	13.33[a] (0.935)	14.88 (0.991)	15.33 (0.577)
Central venous pressure (kPa)	1.29 (0.119)	2.10[a] (0.275)	3.199[b] (0.463)		1.94[ay] (0.190)	0.540[az] (0.119)	1.05[y] (0.230)	1.41[y] (0.123)
Respiratory rate (per min)	9.4 (1.54)	11.5 (2.49)	0.00 (0.00)		15.7[z] (2.24)	23.5[az] (3.66)	27.5 (4.02)	22.7[az] (3.20)
Minute volume* (l/min)	-	9.02 (1.375)	0.00 (0.00)		13.57[z] (2.900)	15.89[az] (2.099)	18.50[a] (3.121)	14.04[z] (2.801)
Arterial carbon dioxide tension (kPa)	5.47 (0.294)	6.08 (0.384)	7.94[b] (0.179)		-	5.44[z] (0.394)	5.36[z] (0.461)	5.31[z] (0.368)
Arterial oxygen tension (kPa)	10.10 (0.220)	7.80[b] (0.292)	4.96[b] (0.456)		-	8.30[ay] (0.653)	8.44[ay] (0.578)	8.65[ay] (0.610)
Venous oxygen tension (kPa)	4.88 (0.181)	4.07 (0.397)	2.86[b] (0.301)		-	4.43[y] (0.328)	4.13[y] (0.268)	4.86[y] (0.333)
Rectal temperature (°C)	37.9 (0.49)	37.7 (0.54)	37.6 (0.57)		-	36.7 (0.26)	37.0 (0.22)	37.0 (0.23)
Blood glucose (mmol/l)	4.51 (0.133)	5.01 (0.241)	5.12[a] (0.116)		-	5.70[a] (0.306)	4.40[y] (0.143)	4.46[y] (0.164)
Haemoglobin (g/l)	116.7 (7.07)	118.7 (4.80)	115.7 (5.39)		-	118.3 (7.43)	118.0 (7.26)	119.1 (9.16)
Plasma total proteins (g/l)	67.00 (1.64)	65.50 (0.86)	65.30 (1.11)		-	66.70 (1.53)	66.50 (0.95)	65.90 (1.32)
Plasma creatinine (μ mol/l)	195 (8.8)	188 (11.1)	201 (6.6)		-	197 (6.8)	189 (4.5)	187 (4.7)

Figures in parantheses indicate standard error of the mean. n = Number of animals.

a = $p < 0.05$; b = $p < 0.01$ -Compared with 0 hour value.

z = $p < 0.05$; z = $p < 0.01$ - Compared with induced ventilatory failure value obtained before administration of prethcamide.

*Minute volume values compared with value at 10 min after anaesthesia.

Cardiovascular effects of the prethcamide were evident by 2.81±0.52 min. In four calves there was a rapid increase followed by a decrease in arterial pressure. Subsequently for 15 min values remained relatively ($p<0.05$) lower than the values recorded at 0 hr. During ventilatory failure heart rate had increased ($p<0.05$) but after prethcamide administration it declined ($p<0.05$) at 5 min and then at 15 min interval it again increased ($p<0.05$), however, thereafter it lowered towards normalcy. Central venous pressure had increased during ventilatory failure and prethcamide administration decreased it ($p<0.05$; $p<0.01$). For initial 15 min these CVP values were much lower ($p<0.05$) than the 0 hour values (See table.V).

A calf (No.84R03) developed junctional rhythm with occasional premature ventricular beats during ventilatory failure and at 2 min interval after prethcamide administration there was a run of ectopic beats for 30 s (Fig.8). Thereafter arrhythmia of any kind was not observed during the period of observation. In another calf transient junctional tachycardia was observed during 40 min period. In general the ECG revealed, primary T-wave and ST-segment changes frequently in different recordings.

Rectal temperature, blood haemoglobin, plasma total proteins and plasma creatinine were not affected. Blood glucose remained elevated ($p<0.05$) up to 15 min after prethcamide administration and afterwards values were

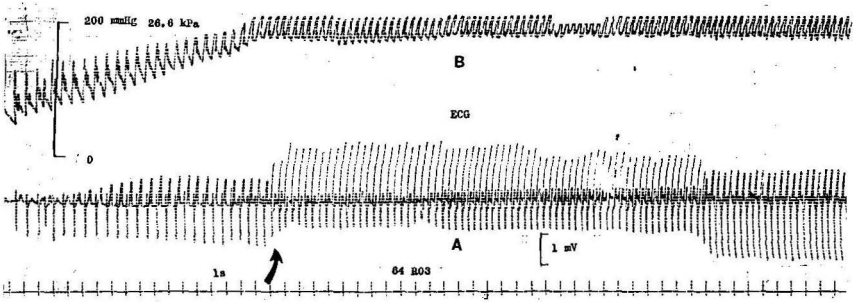

Fig. 8. Run of ventricular tachycardia after prethcamide administration.

A = ECG tracing obtained a 2 min after prethcamide administration. Arrow indicated start of ectopic beats.

B = Simultaneously recorded tracing of arterial pressure. See rise in arterial pressure.

lower ($p<0.05$) as compared to values obtained during ventilatory failure.

8. Nikethamide in ventilatory failure. (Group-VI)

Nikethamide was given i.v. in increments of 2 to 5 ml in buffalo calves with thiopentone induced ventilatory failure. Ventilatory efforts on part of the animal were initiated 2.75±0.87 min (1 to 4.5 min) after start of the nikethamide administration. Initially, deep breaths occurred at an interval of 30 to 60 s. Regular breathing was established by 10.25±2.75 min (5 to 15 min). Only in one animal the periodic deep breathing shifted to jerky rhythm for 15 min. The total dose of 25% nikethamide solution required for restoration of regular breathing was 23.75± 3.393 ml or 95.35±10.66 mg/kg or 0.38 ml/kg.

Corneal and palpebral reflexes starting returning by 15 min in three calves and by 30 min in other two calves. Their return correlated with restoration of electrical activity in the EEG. Pupils remained constricted or there was downward rotation of eye balls. Four calves showed occasional spontaneous flapping of ears and deep pin-pricks would intensify it. In one calf, muscle twitching occurred for initial 15 min. Cutaneous reflex was resumed 30 to 60 min after nikethamide administration.

Electrical activity in the EEG was noticed before 15 min in three calves and in other two by 30 min. There

was a considerable variation in the ECG wave configuration. In two calves, complete electrical silence shifted to high frequency waves with variable amplitude (low or high); while in other three calves, high voltage-high frequency or low voltage-low frequency patterns were seen, at one stage or other during the period of observation.

After regular breathing was established the respiratory rate remained within the normal (0 hr) range. Respiratory minute volume was significantly ($p<0.05$) higher at 15 min recording interval, thereafter, it had a declining trend. However, values remained always higher in comparison to the recordings made after initial thiopentone anaesthesia, when they were breathing spontaneously. At 15 min after nikethamide administration the arterial pCO_2 was higher ($p<0.05$) than 0 hr values but significantly ($p<0.05$) lower than the values obtained during ventilatory failure. Thereafter the carbon dioxide tension returned to normalcy. A marked rise ($p<0.05$; $p<0.01$) in the arterial and the venous pO_2 was evident by 15 min after nikethamide administration (Table-VI).

In three animals each increment of the nikethamide caused transient rise in arterial pressure and heart rate. The nikethamide initiated such cardiovascular changes by 48 ± 10.12 s. In these three calves there was an average rise ($p<0.05$) in MAP from 15.23 ± 0.697 kPa or 114.24 ± 5.23 mmHg (values recorded during later stages of ventilatory failure

Table VI: The effects of nikethamide @ 95.4±11 mg/kg i.v. following thiopentone sodium induced ventilatory failure in buffalo calves (Group-VI).

parameter (units)	0 hour	Thiopentone administration		Minutes after nikethamide administration				
		10 min after anaesthesia	Induced ventilatory failure I	II	15	30	45	60	75
	n=5	n=5	n=5	n=5	n=5	n=5	n=5	n=5	n=4
Heart rate (per min)	45.1 (5.25)	53.8 (4.55)	50.4 (5.64)	92.1 (7.44)	65.8 (7.08)	49.8^{y} (2.66)	51.43^{y} (4.95)	54.16^{y} (4.30)	55.0^{y} (3.81)
Mean arterial pressure (kPa)	17.22 (0.439)	15.99 (0.460)	6.22^{b} (0.521)	16.99 (0.713)	17.50 (0.474)	15.44 (0.909)	14.38^{ay} (0.592)	14.44^{ay} (0.523)	14.94^{a} (0.760)
Systolic pressure (kPa)	18.99 (0.439)	17.66 (0.459)	7.99^{b} (0.608)	18.99 (0.769)	19.83 (0.299)	17.33 (0.832)	16.49^{a} (0.565)	16.66^{a} (0.414)	17.49 (0.565)
Diastolic pressure (kPa)	16.33 (0.439)	15.16 (0.286)	6.33^{b} (0.550)	15.99 (0.754)	16.33 (0.560)	14.50 (0.708)	13.33^{a} (0.599)	13.33^{a} (0.826)	13.66^{a} (0.728)
Central venous pressure (kPa)	1.13 (0.197)	1.86^{a} (0.103)	3.51^{a} (0.443)		0.915^{z} (0.273)	1.25^{y} (0.248)	1.45^{y} (0.334)	1.27^{y} (0.381)	1.21^{y} (0.376)
Respiratory rate (per min)	16.2 (1.38)	16.0 (2.40)	0.00 (0.00)		18.7^{z} (3.30)	15.0^{z} (2.66)	13.2^{z} (1.91)	13.7^{z} (2.25)	13.0^{z} (1.96)
Minute volume* (l/min)	-	6.82 (0.483)	0.00 (0.00)		12.67^{az} (1.291)	10.23^{z} (2.480)	8.43^{z} (1.367)	8.53^{z} (1.117)	9.33^{z} (2.053)
Arterial carbon dioxide tension (kPa)	5.32 (0.091)	6.58^{b} (0.397)	8.20^{b} (0.582)		6.66^{ay} (0.373)	5.97^{y} (0.341)	5.53^{z} (0.192)	5.40^{z} (0.273)	5.34^{z} (0.264)
Arterial oxygen tension (kPa)	9.35 (0.319)	7.24^{a} (0.445)	4.11^{b} (0.356)		8.59^{z} (0.445)	8.06^{z} (0.447)	8.09^{z} (0.562)	8.49^{z} (0.460)	8.50^{z} (0.542)
Venous oxygen tension (kPa)	4.74 (0.133)	3.76^{a} (0.382)	2.16^{b} (0.267)		4.96^{z} (0.317)	4.31^{y} (0.385)	3.99^{ay} (0.611)	3.71^{ay} (0.327)	3.89^{y} (0.343)
Rectal temperature (°C)	38.3 (0.79)	38.0 (0.79)	37.9 (0.80)		37.5 (0.82)	37.5 (0.79)	37.4 (0.76)	37.4 (0.77)	37.4 (0.73)
Blood glucose (mmol/l)	4.02 (0.201)	5.20^{a} (0.355)	5.13^{a} (0.354)		5.32^{a} (0.407)	4.61 (0.353)	4.34 (0.434)	4.19 (0.442)	3.68^{y} (0.368)
Haemoglobin (g/l)	102.6 (7.98)	101.8 (9.25)	101.3 (6.40)		107.0 (8.30)	101.5 (7.55)	96.7 (8.17)	100.0 (6.59)	100.5 (8.74)
Plasma total proteins (g/l)	78.30 (2.78)	77.50 (1.71)	74.50 (1.95)		76.00 (1.16)	75.30 (1.54)	74.00 (2.41)	75.20 (1.43)	74.20 (2.19)
Plasma creatinine (µ mol/l)	148 (14.6)	152 (11.1)	163 (8.9)		159 (13.7)	161 (12.6)	170 (26.6)	172 (17.5)	171 (19.8)

Figures in parentheses indicate standard error of the mean. n = Number of animals.

a = $p < 0.05$; b= $p < 0.01$ - Compared with 0 hour value.

y = $p < 0.05$; z= $p < 0.01$ - Compared with induced ventilatory failure value obtained before administration of nikethamide.

*Minute volume values compared with value at 10 minute after anaesthesia.

and before nikethamide administration) to 19.75±1.067 kPa (148.2±8.01 mmHg). Similarly, heart rate increased from 99.2±2.2 to 127±3.4/min ($p<0.01$) (Fig.9). During this tachycardia, there were primary T-wave and ST-segment changes. In other two calves MAP remained relatively unaffected but transient increase in heart rate i.e. from 76.2 to 122.1/min was observed. Arterial pressure decreased ($p<0.05$) after 30 min in all the animals. Central venous pressure which had markedly increased during the ventilatory failure was decreased ($p<0.05$) after nikethamide administration and returned near 0 hr values subsequently. (See table-VI).

In one calf AV-dissociation with acceleration and occasional hypodynamic premature ectopic beats were observed between 50 to 55 min after nikethamide administration (Fig.10).

There were no significant changes in rectal temperature, blood haemoglobin, plasma total proteins and plasma creatinine. Blood glucose remained elevated upto 15 min and thereafter returned to 0 hr level (See table-VI).

Calf No.83C03 died 70 min after nikethamide administration. In this calf, ventilatory efforts were initiated 90 s after start of nikethamide administration and by 7.5 min regular breathing was established. Cutaneous and eye reflexes had returned by 30 min. At 60 min interval, respiratory minute volume was 5.8 l/min

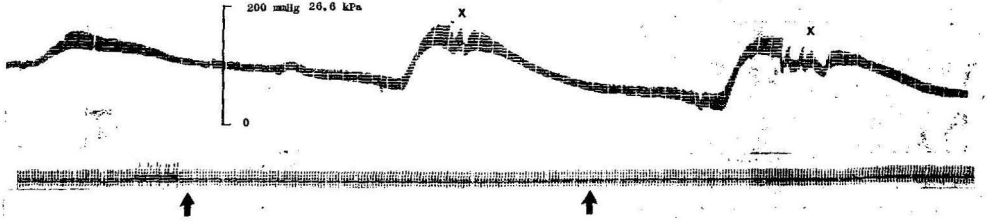

Fig. 9. Arterial pressure changes subsequent to nikethamide administration in a buffalo calf under deep thiopentone anaesthesia.

Arrow indicates i.v. administrations of 5ml of nikethamide solution.
X= Arterial pressure fluctuations during deep respirations.

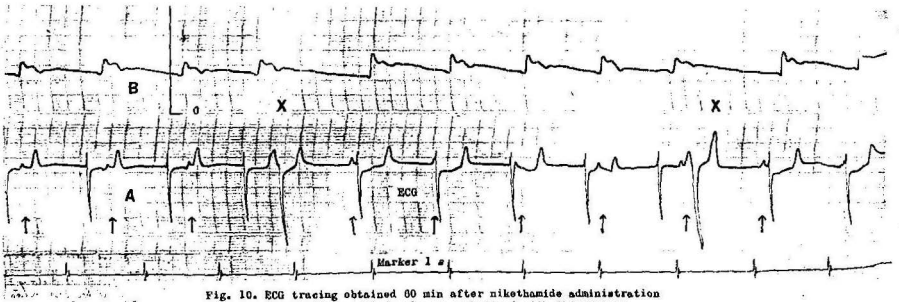

Fig. 10. ECG tracing obtained 90 min after nikethamide administration in a buffalo calf deeply anaesthetized with thiopentone.

A = Showing AV-dissociation with accrochage. Arrow indicates P-waves and see their wandering in and out of the QRS complex.

B = Simultaneous arterial pressure recording. X indicates ineffective premature ectopic beat.

against the 6.0 l/min recorded after thiopentone anaesthesia with spontaneous ventilation. At 70 min after nikethamide administration, suddenly ventilatory efforts ceased, calf struggled and died. This calf had developed junctional tachycardia during ventilatory failure which was however abolished by nikethamide administration. Subsequently this calf did not develop any arrhythmia until this terminal event. Arterial pressure remained always near normal i.e. at 60 min MAP was 14.07 kPa against the 0 hr value of 15.32 kPa. There was no evidence of circulatory failure before this ventilatory failure occurred.

9. Mephentermine and prethcamide in circulatory insufficiency with ventilatory failure. (Group VII)

In these animals when additional doses of thiopentone were given to induce circulatory insufficiency the MAP decreased from 13.88±0.878 kPa (104.16±6.59 mmHg) to 5.94±0.904 kPa (44.58±6.78 mmHg). Accompanied ventilatory failure was not supported mechanically. Intravenous administration of mephentermine (0.5 mg/kg) was followed by prethcamide (9 mg/kg).

Ventilatory efforts were initiated within 1.6±0.37 min after prethcamide administration. In three calves initial deep breathing was replaced by periodic or jerky type breathing for 15 min. All calves had regular breathing thereafter. After prethcamide administration within 5 min eye reflexes returned and eyelids remained half close. In three calves, frequent unprovoked ear flapping was observed

upto 15 min and subsequently decreased in intensity with the time. Two calves among these three, exhibited typical excitement, pin-pricks would aggravate ear flapping, initiate cutaneous reflex and movement of limbs. All calves by 60 min had eyes wide open and appeared to be awake.

Electrical activity in the EEG was resumed 2.77± 0.92 min after nephentermine and prethcamide administration. Study of the EEG wave configuration revealed, that two types of patterns were present. High voltage-high frequency pattern was associated with ear flapping, but whenever animals were calm and without any sign of excitation, a complex wave form was observed (Fig.11).

Cardiovascular effects of nephentermine started 0.63±0.12 min after its administration and by 1.44±0.24 min it had its transient peak effect. In three calves after prethcamide administration there was further increase in arterial pressure by 5.99±1.232 kPa (45.00± 9.25 mmHg) while in other two calves it did not evoke any such pressure response. Heart rate increased markedly ($p<0.01$) after nephentermine and prethcamide administration. Values were higher than those recorded during the circulatory insufficiency and at 0 hr. Hypotension induced by thiopentone was ameliorated by nephentermine and prethcamide. Arterial pressure remained within normal range during the entire period of study.

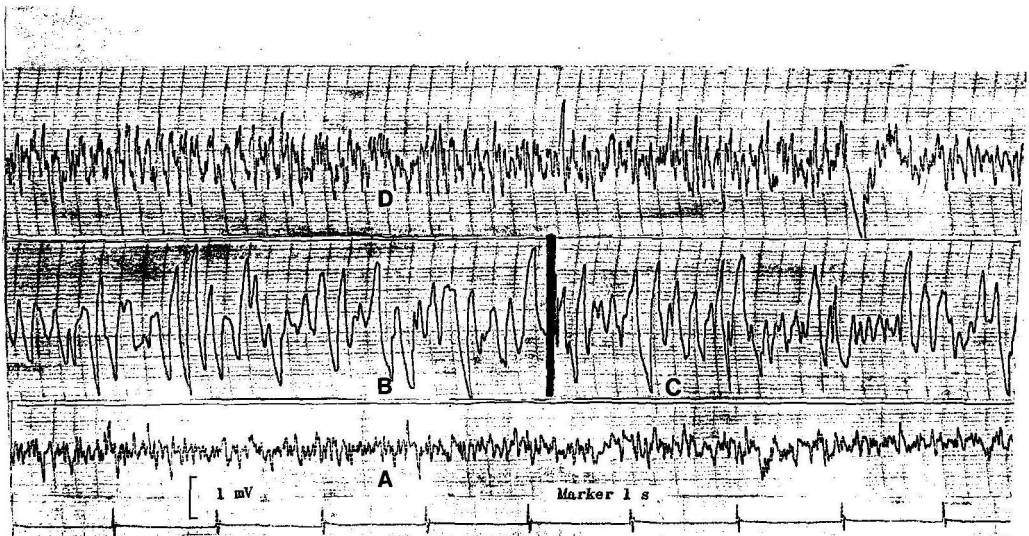

Fig. 11. EEG wave patterns after mephentermine and prethcamide administration in a buffalo calf with thiopentone induced circulatory insufficiency and ventilatory failure.

A = Tracing obtained before administration of thiopentone (0 hr). Showing low voltage-high frequency pattern.

B = After thiopentone given 'to-effect' i.e. routine anaesthesia. Showing typical complex wave form (Courtin's level-3).

C = Tracing obtained 10 min after mephentermine and prethcamide administration. Animal was calm and not flapping its ears. See typical complex wave form, compare with tracing-B.

D = Tracing obtained 5 min later when unprovoked ear flapping started. See high voltage-high frequency pattern, compare with tracing-A.

except a noticeable hypertension ($p<0.05$) at 5 min after administration of these drugs. Elevated CVP was decreased ($p<0.01$), and at 5 min and 75 min interval CVP was much lower ($p<0.05$) than the 0 hr values (Table-VII).

After mephentermine and prethemamide administration any major arrhythmia was not observed. Calf No.23MR03 had II-degree AV-block, type-II earlier during circulatory insufficiency and was abolished by mephentermine administration. Primary T-wave changes and sinus arrhythmia during deep breathing were observed frequently.

Respiratory rate and minute volume remained higher ($p<0.05$) than their respective base values, after mephentermine and prethemamide administration. Increased carbon dioxide tension in the arterial blood was reduced remarkably ($p<0.05$) by 15 min and the arterial oxygen tension was increased ($p<0.05$) by 5 min, after mephentermine and prethemamide administration. Venous oxygen tension was also restored to normalcy (See Table-VII).

The elevated blood glucose, recorded following thiopentone administration, was further increased following administration of mephentermine and prethemamide. However, blood glucose values returned to normal before experiment was terminated. There were no changes in rectal temperature, blood haemoglobin, plasma total proteins and plasma creatinine (see Table-VII).

Table VII: The effects of mephentermine @ 0.5 mg/kg and prethcamide 9 mg/kg i.v. following thiopentone sodium induced circulatory insufficiency and ventilatory failure (CIVF) in buffalo calves (Group VII).

Parameter (units)	0 hour	Thiopentone administration		Minutes after mephentermine and nikethamide administrat					
		10 min after anaesthesia	Induced CIVF	5	15	30	45	60	75
	n=6	n=6	n=6	n=6	n=6	n=6	n=6	n=6	n=6
Heart rate (per min)	45.4 (4.31)	58.6 (5.21)	59.6[a] (2.58)	137.9[bz] (8.18)	88.4[ay] (9.65)	79.6[ay] (7.81)	79.0[ay] (7.00)	76.5[ay] (6.06)	68.0[a] (6.32)
Mean arterial pressure (kPa)	15.83 (0.491)	13.88 (0.878)	5.94[b] (0.904)	20.94[az] (0.583)	17.33[z] (0.444)	16.49[z] (0.574)	15.55[z] (0.728)	14.88[z] (0.629)	14.44[z] (0.392)
Systolic pressure (kPa)	18.49 (0.557)	15.66[a] (0.430)	7.49[b] (0.858)	22.83[bz] (0.574)	19.66[z] (0.432)	18.16[z] (0.601)	17.33[z] (0.698)	16.66[z] (0.463)	16.33[az] (0.326)
Diastolic arterial pressure (kPa)	14.49 (0.601)	12.99 (0.333)	5.16[b] (0.865)	19.99[bz] (0.549)	16.16[z] (0.531)	15.66[z] (0.586)	14.66[z] (0.594)	13.99[z] (0.440)	13.49[z] (0.319)
Central venous pressure (kPa)	1.08 (0.197)	1.67 (0.119)	3.31[b] (0.324)	0.39[az] (0.124)	0.58[z] (0.277)	0.61[z] (0.215)	0.53[z] (0.368)	0.41[z] (0.234)	0.19[az] (0.229)
Respiratory rate (per min)	15.0 (1.41)	15.3 (2.36)	0.0 (0.00)	37.0[az] (4.76)	22.9[az] (2.31)	28.8[az] (3.75)	28.5[az] (2.98)	29.8[az] (3.11)	30.0[az] (4.40)
Minute volume* (l/min)	-	5.97 (1.584)	0.00 (0.00)	14.30[az] (1.344)	12.24[az] (1.154)	12.34[az] (1.142)	13.19[az] (2.010)	13.08[az] (1.948)	14.48[az] (1.606)
Arterial carbon dioxide tension (kPa)	4.95 (0.120)	5.06 (0.568)	8.05[b] (0.581)	7.03[a] (0.441)	6.34[ay] (0.332)	5.91[y] (0.394)	5.10[z] (0.133)	5.08[y] (0.203)	5.02[y] (0.232)
Arterial oxygen tension (kPa)	9.99 (0.262)	7.47[b] (0.371)	5.09[b] (0.648)	8.81[y] (0.501)	8.78[ay] (0.421)	8.31[ay] (0.640)	8.24[ay] (0.594)	8.19[ay] (0.661)	8.38[y] (0.781)
Venous oxygen tension (kPa)	5.06 (0.191)	4.56 (0.423)	2.63[b] (0.037)	5.04[z] (0.127)	5.01[z] (0.089)	4.39[z] (0.161)	4.39[z] (0.161)	4.36[z] (0.199)	4.33[z] (0.195)
Rectal temperature (°C)	37.4 (0.64)	36.9 (0.66)	36.9 (0.62)	-	36.7 (0.70)	36.6 (0.69)	36.8 (0.59)	37.0 (0.47)	37.1 (0.50)
Blood glucose (mmol/l)	4.90 (0.222)	6.06[a] (0.287)	6.19[a] (0.332)	-	7.33[a] (0.478)	6.75[a] (0.419)	5.58 (0.333)	5.36 (0.418)	4.91[y] (0.337)
Haemoglobin (g/l)	101.6 (10.58)	98.6 (8.67)	97.3 (9.12)	-	101.3 (9.13)	101.0 (10.11)	98.6 (9.03)	95.7 (9.84)	98.3 (10.93)
Plasma total proteins (g/l)	74.00 (2.00)	73.30 (0.68)	70.30 (2.18)	-	72.30 (2.01)	74.30 (1.15)	74.20 (1.52)	74.00 (2.16)	73.90 (1.06)
Plasma creatinine (μ mol/l)	203 (22.3)	209 (26.2)	221 (35.7)	-	253 (19.3)	218 (12.4)	235 (15.6)	239 (8.8)	203 (11.5)

Figures in parentheses indicate standard error of the mean. n = Number of animals.

a = $p < 0.05$; b = $p < 0.01$ -Compared with 0 hour value.

y = $p < 0.05$; z = $p < 0.01$ -Compared with induced circulatory insufficiency and ventilatory failure (CIVF) value obtained before administration of mephentermine and prethcamide.

*Minute volume values compared with value at 10 min after anaesthesia.

10. Norepinephrine and nikethamide in circulatory insufficiency with ventilatory failure (VIII)

When arterial pressure was reduced to 5.72±0.47 kPa (42.8±3.53 mmHg) by additional increment of thiopentone, the accompanied ventilatory failure was not supported mechanically. Norepinephrine drip (4 µg/ml) was started and 25% nikethamide solution was given in increments of 3 to 5 ml. Total dose of nikethamide solution required for establishing regular ventilatory efforts was 17.50± 4.38 ml or 80.69±23.82 mg/kg or 0.3% ml/kg. Ventilatory efforts started initially with deep breaths by 1.88±0.27 min (0.5 to 4 min) and regular breathing was established by 5.38±1.88 min after start of nikethamide administration. In one calf periodic ventilatory efforts were initiated but regular breathing could not be restored and calf died consequently.

In three calves eye reflexes were restored by 5 min, cutaneous reflex and movement in response to deep pin-pricks were observed within 15 min after nikethamide administration. In other two calves resumption of reflex activity started by 30 min. In all calves occasional unprovoked ear flapping was observed, pupils were either constricted or there was downward rotation of eye balls. Only one calf exhibited typical excitement, more intense ear flapping and movement of tail was observed. This calf would struggle for restraint in response to deep pin-pricks.

Electrical activity in the EEG was noticeable, within 10 min in all the surviving calves. Initially, there was complex wave form or predominantly high voltage-low frequency pattern, subsequently frequency increased and amplitude of the waves remained either relatively same or decreased moderately. Unprovoked ear flapping and movement of the tail was associated with high voltage-high frequency pattern in the EEG.

Cardiovascular effects of norepinephrine started 0.82±0.13 min after start of the drip. Near normal range of the arterial pressure could be achieved by 1.28±0.21 min, and this was much earlier ($p<0.05$) than, when norepinephrine was given alone, as in group-III. Each increment of nikethamide caused further but transient increase by 8.38±1.22 kPa (62.14±9.57 mmHg) in mean arterial pressure.

Initially, heart rate increased during norepinephrine drip and after nikethamide administration but by 15 min it stabilised to near normal values. When norepinephrine infusion was stopped, heart rate remained above 0 hr values for 30 min. The arterial pressure had an undulatory trend initially. At 5 min interval and subsequently during norepinephrine infusion arterial pressure remained within normal range, and was obviously above ($p<0.01$) the induced hypotensive values recorded during circulatory

insufficiency. Once norepinephrine infusion was stopped i.e. after 30 min, arterial pressure decreased. Values were lower than 0 hr values ($p<0.05$) but higher than the induced hypotensive values. Central venous pressure had increased during circulatory insufficiency and ventilatory failure. Norepinephrine and nikethamide brought the values within 0 hr ranges (Table-VIII).

Electrocardiographic monitoring revealed primary T-wave and ST-segment changes. One calf developed transient AV-dissociation with ventricular discharge during nikethamide administration.

Respiratory rate and minute volume remained within their respective base value levels. After norepinephrine infusion was discontinued, respiratory rate increased. Arterial pCO_2 and pO_2 venous pO_2 were all restored to 0 hr values (see table-VIII).

The elevated blood glucose recorded during circulatory insufficiency and ventilatory failure was further increased for 45 min and thereafter values had a trend to return to normalcy. There were no changes in rectal temperature, blood haemoglobin, plasma total proteins and plasma creatinine (see table-VIII).

In calf No.12 $NaHCO_3$ regular breathing could not be restored. Norepinephrine drip had its cardiovascular response by 60 s and each nikethamide increment of 5 ml

Table VIII: The effects of norepinephrine drip (4 µg/ml) and nikethamide @ 81+24 mg/kg i.v. following thiopentone sodium induced circulatory insufficiency and ventilatory failure (CIVF) in buffalo calves (Group-VIII).

Parameter (units)	0 hour	Thiopentone administration		Minutes after start of norepinephrine drip and nikethamide administration			Minutes after disconnecting drip		
		10 min after anaesthesia	Induced CIVF	5	15	30	15	30	45
	n=5	n=5	n=5	n=5	n=4	n=4	n=4	n=4	n=4
Heart rate (per min)	44.6 (1.29)	48.8 (2.22)	51.3 (3.92)	76.8^{by} (5.59)	48.6 (2.30)	48.5 (1.52)	55.2^{a} (2.46)	57.1^{a} (4.43)	55.7 (7.10)
Mean arterial pressure (kPa)	16.49 (0.434)	14.78 (0.572)	5.72^{b} (0.480)	16.52^{z} (0.647)	14.22^{z} (0.742)	14.16^{z} (0.936)	11.78^{bz} (0.323)	10.81^{bz} (0.445)	11.78^{bz} (0.769)
Systolic pressure (kPa)	18.83 (0.420)	16.67^{a} (0.576)	8.67^{b} (0.544)	17.99^{z} (0.577)	15.99^{az} (0.800)	15.78^{az} (0.999)	13.55^{bz} (0.326)	12.44^{bz} (0.459)	12.55^{bz} (0.769)
Diastolic pressure (kPa)	15.33 (0.416)	13.83 (0.667)	4.83^{b} (0.272)	15.78^{z} (0.581)	13.33^{z} (0.867)	13.33^{z} (0.909)	10.89^{bz} (0.608)	9.999^{bz} (0.162)	10.88^{bz} (0.732)
Central venous pressure (kPa)	1.41 (0.227)	2.10 (0.267)	3.92^{a} (0.303)	1.18^{z} (0.199)	1.78^{z} (0.235)	1.99^{y} (0.237)	1.67^{z} (0.175)	1.08^{z} (0.206)	1.07^{z} (0.240)
Respiratory rate (per min)	9.5 (0.86)	12.8 (3.45)	0.00 (0.00)	16.3^{az} (2.64)	11.3^{z} (2.58)	12.7^{z} (1.26)	14.3^{az} (1.83)	16.0^{az} (1.01)	15.7^{az} (0.26)
Minute volume* (l/ min)	-	4.60 (0.797)	0.00 (0.00)	9.47^{az} (1.345)	5.33^{z} (0.832)	5.47^{z} (0.232)	5.77^{z} (0.828)	7.28^{z} (0.878)	7.67^{z} (0.763)
Arterial carbon dioxide tension (kPa)	4.94 (0.251)	5.49 (0.358)	9.85^{b} (0.480)	6.74^{ay} (0.392)	5.34^{z} (0.479)	5.45^{z} (0.525)	5.21^{z} (0.224)	4.68^{z} (0.172)	4.85^{z} (0.198)
Arterial oxygen tension (kPa)	10.69 (0.365)	6.95^{a} (0.464)	4.18^{b} (0.479)	8.37^{ay} (0.588)	9.48^{z} (0.549)	9.07^{z} (0.677)	9.10^{z} (0.703)	8.06^{z} (0.678)	8.16^{z} (0.671)
Venous oxygen tension (kPa)	5.16 (0.196)	5.68^{a} (0.360)	2.63^{b} (0.037)	4.13^{a} (0.446)	5.57^{z} (0.371)	5.23^{z} (0.282)	4.93^{z} (0.079)	4.85^{z} (0.078)	4.63^{z} (0.212)
Rectal temperature (°C)	37.1 (0.30)	37.0 (0.32)	37.0 (0.30)	-	37.2 (0.45)	37.3 (0.49)	37.0 (0.39)	37.0 (0.39)	37.0 (0.48)
Blood glucose (mmol/l)	3.90 (0.166)	4.60 (0.168)	4.48^{a} (0.140)	-	5.13^{by} (0.139)	5.13^{ay} (0.192)	5.62^{ay} (0.278)	4.99^{a} (0.423)	4.88 (0.468)
Haemoglobin (g/l)	115.7 (4.02)	114.5 (5.67)	116.0 (5.81)	-	113.0 (3.06)	110.1 (3.01)	109.6 (3.93)	111.6 (5.49)	109.6 (6.96)
Plasma total proteins (g/l)	78.30 (1.25)	78.30 (0.25)	72.70 (3.21)	-	72.00 (3.00)	75.00 (1.42)	72.20 (3.91)	75.70 (2.00)	76.20 (1.25)
Plasma creatinine (µ mol/l)	170 (10.7)	194 (43.6)	162 (25.9)	-	185 (32.7)	176 (17.7)	212 (25.9)	176 (18.6)	185 (8.8)

Figures in parentheses indicate standard error of the mean. n = Number of animals.

a = $p < 0.05$; b = $p < 0.01$ - Compared with 0 hour value.

y = $p < 0.05$; z = $p < 0.01$ - Compared with induced circulatory insufficiency and ventilatory failure (CIVF) values obtained before starting norepinephrine drip and nikethamide administration.

*Minute volume values compared with value at 10 min after anaesthesia.

increased the arterial pressure by 6.67 kPa (50 mmHg) and 10.00 kPa (75 mmHg) respectively. Within 30 s after 10 ml of nikethamide had been administered, first ventilatory response characterised by deep breaths, with a frequency of 2 to 3/min was observed. Further administration of nikethamide (total of 40 ml in increments) did not establish regular breathing. There were occasional gasps for 8 min. Electroencephalograms remained flat. Arterial pressure changes were undulatory for 8 min and thereafter progressive fall was observed. Finally arterial pressure reached to 1.32 kPa (10 mmHg) and electrical activity (junctional rhythm) did not evoke mechanical response. Animal died.

DISCUSSION

Systemic, detailed investigations concerning the effects of various sympathomimetic drugs, analeptics and corticosteroids in buffaloes are few and most of the reports available are on other species. Therefore, observations of our present experiments are discussed with these available reports, however, attempt has been made to take necessary precautions while extrapolating results from other species.

The study under consideration, was done on 40 buffalo calves, divided in eight groups of five animals each. After establishing the base line values (0 hr) for different parameters in all calves, thiopentone was given 'to-effect' and observations were made. These observations in all the groups are discussed under one head. The animals in six experimental groups (I, II, III, IV, VII & VIII) received additional doses of thiopentone to induce circulatory insufficiency. Whereas, group-I animals (control) were not given any other drug, the animals of other five groups received various drugs/drug combinations either to reverse the ventilatory failure and/or to support the circulatory insufficiency. Observations made before administration of any drug, or during circulatory insufficiency in these groups are discussed together under a separate heading. In remaining two groups (V & VI) thiopentone was further administered until ventilatory failure occurred. Observations made during ventilatory failure and before administration of

analeptics are also discussed separately. Effects of drugs, administered to support circulation and/or ventilation are discussed separately for each drug or combination. Thus observations of the present study are discussed under following headings:

1. Thiopentone given 'to-effect'. (Groups- I to VII, n=40)
2. Thiopentone induced circulatory insufficiency and control. (Groups- I, II, III, IV, VII & VIII, n=30)
3. Thiopentone induced ventilatory failure. (Groups- V & VI, n=10)
4. Mephentermine in circulatory insufficiency. (Group-II)
5. Norepinephrine in circulatory insufficiency. (Group III)
6. Dexamethasone in circulatory insufficiency. (Group IV)
7. Prethcamide in ventilatory failure. (Group-V)
8. Nikethamide in ventilatory failure. (Group-VI)
9. Mephentermine and prethcamide in circulatory insufficiency with ventilatory failure. (Group-VII)
10. Norepinephrine and nikethamide in circulatory insufficiency with ventilatory failure. (Group-VIII)

1. Thiopentone given 'to-effect'. (Groups- I to VIII, n=40)

Considerable work has been done with thiopentone anaesthesia in buffaloes. Its use alone and in combination with various preanaesthetic medications is reported (Mirakhur et al., 1980; Singh et al., 1980; Nigam et al., 1983; Peshin and Nigam, 1985; Peshin et al., 1986).

Thiopentone is known to produce general anaesthesia by suppression of ascending reticular activating system in

the brain. Anaesthetic responses observed in the present study (see page 26) are contiguous to earlier reports (Peshin and Nigam, 1986). In our experiments, Courtin's level-3 in EEG was a consistent feature during thiopentone anaesthesia. Almost similar wave patterns have been recorded in adult buffaloes anaesthetised with thiopentone and undergoing major surgery (Peshin and Nigam, 1985). This confirms association of these EEG patterns with surgical anaesthesia. Recently, Frank et al. (1984) have described correlation between free thiopentone concentrations and mean EEG amplitudes. They found that, low amplitude-high frequency pattern (beta rhythm) was negatively correlated, while high amplitude-low frequency pattern (delta rhythm) was positively correlated with log of free thiopentone concentration in blood.

Among cardiovascular parameters, the major change was an increase in central venous pressure after thiopentone administration. This could be due to positive pressure ventilation and or myocardial depression due to thiopentone itself. Calves of groups-I, II, III & IV were ventilated with positive pressure. The forcible expansion of the lungs during positive pressure ventilation might compress the heart and great veins and the cardiac output may suffer (Price et al., 1952). Increased mean airway pressure with approximately 1:1 inspiratory and expiratory ratio decreases

the venous return to the heart (Morgan et al., 1966) and reduces pulmonary blood flow with concomittent increase in pulmonary pressure and resistance, during positive inspiratory phases (Edwards, 1951). A marked rise in CVP after the start of positive pressure ventilation, subsequent to thiopentone administration had been reported in adult buffaloes (Peshin et al., 1986). Spontaneously breathing calves, after thiopentone administration from other four groups (i.e. V, VI, VII & VIII) also had elevated CVP. Decreased efficiency of the heart to pump out the blood brought by greater veins would increase CVP irrespective of ventilatory status. Barbiturates basically tend to depress myocardium and partially inhibit ganglionic transmission leading to hypotension. In an intact animal, relatively unaffected baroreceptor mediated responses operate for compensation and evoke sympathoadrenal output accordingly. Either there is centrally induced increase in total peripheral vascular resistance over-riding the ganglionic inhibition and/or increase in heart rate. Their degree of compensation decides the haemodynamic status of the animal during barbiturate anaesthesia.

A perusal of our data reveal that, when thiopentone is administered in recommended doses or given 'to-effect', there is a tendency in heart rate to increase and a tendency in MAP to decrease. However, the values remain within the normal limits. It has been emphasised in the preceding

paragraph, that the haemodynamic changes would depend on a balance between pharmacological actions of the thiopentone and the sympathoadrenal responsiveness of the recipient. Thus, one need not attach much clinical significance to the mentioned changes in HR, MAP and CVP. Should the doses of thiopentone be increased considerably, aggravation of these changes would jeopardise the homeostasis of haemodynamics.

In one animal II-degree AV-block developed after thiopentone administration and is suggestive of parasympathetic stimulation of the myocardial conduction system. These types of AV-block do occur normally in healthy cattle and were also observed in the present study.

The primary T-wave and ST-segment changes as seen frequently in our study, are the commonest type of ECG changes observed during administration of various anaesthetics in different species and has been explained by Peshin et al. (1985). ST-segment and T-wave represent the repolarisation of ventricles, during which sodium ion efflux takes place actively. This active mechanism of Na^+-K^+ pump involves metabolic work and the action of ATPase; and is more readily affected by altered electrolyte concentrations and oxygen tension in the myocardium. Because of this, the repolarisation part of the action potential of myocardium is much more readily altered by even small changes in myocardial interior milieu while depolarisation part (P-wave and QRS complex) which involves passive transport remains relatively unaltered.

Changes in blood gases were predictable. In spotaneously breathing calves mild hyperocapnia and hypoxemia was present, obviously due to respiratory depressant action of the thiopentone.

2. Thiopentone induced circulatory insufficiency and control. (Groups- I, II, III, IV, VII & VIII, n=30)

In our experiments when an additional amount (147%) of thiopentone was administered in already anaesthetised calves, there was a marked reduction (by 69%) in arterial pressure. This indicate that about 2.5 times the normal dose of thiopentone would cause circulatory insufficiency in buffalo calves.

Circulatory insufficiency was characterised by marked hypotension, complete suppression of electrical activity in EEG and pupillary dilatation. Similar signs have been also reported by various workers in other species (Palich and Gordon, 1967; Clark, 1977; Gilroy et al., 1980, Ross and Bremnock, 1981).

Electroencephalograms were flat and electrical activity started only after there was a considerable rise in the arterial pressure. Hamlin et al. (1965) reported complete suppression of cortical activity followed by medullary paralysis due to excessive depression by sodium pentobarbitone in dogs. In a more recent study Thomas et al. (1985) have found that decreasing MAP is positively correlated with EEG voltage. An isoelectric EEG and hypotension after pentobarbitone in dogs was associated with about 42% decrease

in cerebral blood flow and 28% decrease in cerebral metabolic rate for oxygen (Lafferty et al., 1978). Thiopentone and xylazine when given in clinical doses maintains the brain oxygen extraction in cattle (Peshin et al., 1982; Singh et al., 1985). Intrinsic autoregulatory mechanisms maintain cerebral blood flow irrespective of changes to some extent in systemic arterial pressure. Since the MAP was 5.45±0.211 kPa (40.9±1.59 mmHg) in the present experiments it appears that the autoregulatory mechanisms would not have operated. Because, when the pressure would fall below 8 kPa (60 mmHg) or when cardiac output falls below 3 l/min in man, the cerebral circulation itself becomes insufficient (Bell et al., 1980). Moreover, deep anaesthesia with barbiturates itself would reduce cerebral blood flow (McDowall, 1980). The observed electrical silence in our experiments during circulatory insufficiency thus appears to be mainly due to the decreased cerebral blood flow.

Hypotension was associated with a mild increase in heart rate and marked increase in CVP. Cardiac output and venous return are inextricably interdependent. Central venous pressure indicate ability of the heart to pump the venous return. Thiopentone causes decrease in the cardiac output and stroke volume in buffaloes (Sobti et al., 1982). Thus in the present study thiopentone overdosage induced a profound myocardial depression and consequently circulatory insufficiency. Such an explanation agrees with that of

Price (1971). Baroreceptor reflexes should have operated in response to hypotension. It appears that such reflexes were either abolished due to excess of thiopentone or hypotension was too low to elicit any response. In dog and cat 5.33 kPa (40 mmHg) is below threshold of the majority of baroreceptors (Smith and Hamlin, 1977).

In calves of groups VII and VIII the accompanied hypoxemia and hypercapnia did not elicit chemoreceptor response to elevate the arterial pressure. It is well known, that deep barbiturate anaesthesia will abolish the blood pressure rise in response to endogenous carbon-dioxide (Dundee and Wyant, 1974a). Hypoxemia and hypercapnia in such circumstances would contribute to the direct depression of myocardium.

Keeping in view the above facts, III-degree AV-block observed in one animal would be due to the direct effect of thiopentone, however, the possibility of parasympathetic stimulation of the cardiac conduction system cannot be ruled out. It may be mentioned here, that the direct myocardial depression can occur without important cardiac electrophysiologic change and yet electromechanical dissociation may be such that the cardiac impulse does not elicit adequate mechanical response.

Blood glucose levels had a tendency to increase further after thiopentone overdose, but the increase was more pronounced in calves where ventilatory failure persisted.

Hyperglycaemia during thiopentone anaesthesia in man (Dundee and Wyant, 1974-a), dog (Brooker et al., 1949, 1952) and horses (Tyagi et al., 1964) has been discussed. Involvement of adrenal glands has been suggested and their removal or inactivation would preclude the peranaesthetic hyperglycaemia (Phillips and Freeman, 1933; Hrubetz and Blackberg, 1938; Johnson, 1949). Hyperglycaemic effects of thiopentone can be mitigated by small doses of insulin (Dundee and Wyant, 1974-a). Level of certain contrainsular hormones is increased during thiopentone anaesthesia with artificial ventilation in buffalo calves (Mirakhur et al., 1982). Hypoinsulinemia has been observed in shock with low cardiac output (Carey et al., 1970; Clowes et al., 1974) and it has been proposed to be due to the result from alpha adrenergic suppression of insulin release from pancreas (Cryer et al., 1972) and diminished pancreatic blood flow (Ferguson et al., 1978). This may explain why there was increased blood sugar level during circulatory insufficiency.

Respiratory depression and carbon dioxide retension are contributory factors for hyperglycaemia during thiopentone anaesthesia (Dundee and Todd, 1968). The affinity of insulin for its receptors can be decreased by acidosis (Harrison et al., 1976; Soman and Felig, 1977). This explains why hyperglycaemia was much higher in calves subjected to retention of carbon dioxide i.e. in groups-V, VI, VII and VIII.

Increase in the arterial pO_2 values was not as high as it should have been, rather a fall during the periods of circulatory insufficiency occurred. Perfusion inequalities in the lung under such circumstances will limit increase in the arterial pO_2 despite positive pressure ventilation. A decrease in cardiac output could be predominantly responsible (Gillespie et al., 1969).

A careful perusal of the data of groups- I, II, III & IV, where ventilation was mechanically controlled, the central venous pO_2 had a declining tendency during the peak hypotensive phase, in spite of the arterial pO_2 values being much higher than the normal values. This would be suggestive of the circulatory insufficiency even at tissue level. Venous pO_2 is more sensitive to cardiac output (Marshall and Wyche, 1972) and would be decreased in spite of above normal arterial pO_2 in low pressure-low flow circulatory states (Peshin et al., 1986). In calves from group-I, where hypotension persisted for 75 min, had a deteriorating trend in venous pO_2.

In five calves (Group-I) the induced circulatory insufficiency was not supported pharmacologically and positive pressure ventilation was constantly carried out. Only two animals survived the period of observation. The major changes were, sustained hypotension, high CVP values and unsatisfactory blood gases.

One calf died 15 min after circulatory insufficiency was induced with thiopentone. Results are suggestive of

circulatory collapse mainly due to myocardial depression and loss of reflex activity to counter it. Fall in venous pO_2 irrespective of satisfactory arterial pO_2 substantiate above conclusion. Other four calves showed some improvement with time but two died because of respiratory failure.

Deteriorating pO_2 and hypercapnia at terminal stages can be related to the relation between oxyhaemoglobin saturation and lung weight (Filmore et al., 1970).

It is concluded that in buffalo calves with circulatory insufficiency due to excess of thiopentone, positive pressure ventilation alone would be of no use.

3. Thiopentone induced ventilatory failure. (Groups- V & VI, n=10)

Thiopentone when given 'to-effect' did not cause apnea, but moderate carbon dioxide retention indicated decreased alveolar ventilation. However, further administration of about 139% thiopentone ensured complete ventilatory failure, characterised by marked hypercapnia and hypoxemia. It appears from the present study that the difference between the doses of thiopentone to induce ventilatory failure and circulatory insufficiency is narrow. Therefore, thiopentone sodium does have a low margin of safety in buffalo calves.

The depression of central nervous system (as judged by reflexes and EEG) was progressive with time, during ventilatory failure and did not show any improvement even after there was reflex increase in arterial pressure. During ventilatory

failure the major changes expected were, hypoxemia and hypercapnia and both are known to accelerate the blood flow to brain. Thiopentone is known to cause a considerable decrease in cerebral blood flow and cerebral oxygen consumption during normal alveolar ventilation in man (Pierce et al., 1962), however, brain oxygen extraction is maintained after thiopentone when administered in clinical doses in cattle (Singh et al., 1985). Even after considering the increase in cerebral blood flow due to severe hypoxemia and hypercapnia, it may not mitigate the cerebral hypoxia. It has been shown that if arterial pO_2 is below 4.27 kPa (32 mmHg) or venous pO_2 is below 2.7 kPa (20 mmHg), unconsciousness and progressive depression of CNS supervene (Anderson et al., 1946; Flynn et al., 1977; Nunn, 1977). Near similar pO_2 values were observed in the present experiments during the period of ventilatory failure. No controlled study about critical pO_2 levels for buffalo brain is available, however, it can be deduced from the results that, EEG changes in the present study are attributive to cerebral hypoxia.

Cardiovascular changes during the period of ventilatory failure were marked. Initial hypotension was ameliorated by compensatory tachycardia. It seems that there were at least three forces to act: one, hypotension itself would decrease discharges from various baroreceptors and consequently releasing inhibition of the vasomotor center with increased sympathoadrenal output to the effector sites. Other two are,

hypoxemia and hypercapnia. Acute hypoxia is known to result in an increase in heart rate, probably mediated through some mechanism other than the carotid and aortic chemoreceptors (Daly and Scott, 1958; Krasney and Koehler, 1977). In buffalo calves increase in arterial pCO_2 up to 21.74±0.21 kPa (163.1± 1.6 mmHg) was positively correlated with MAP with undulatory changes in HR. These changes were attributed to the increased sympathetic adrenergic activity (Peshin et al., 1983). Both hypoxemia and hypercapnia are known to increase circulatory catecholamines in man (Seehzer et al., 1960; Nunn, 1977). Which of these forces, either alone or in combination have operated to normalise the arterial pressure, cannot be concluded from the present study. Moreover, one has to be cautious when results obtained in one species are being extrapolated to another species. However, one thing appears certain, that during the ventilatory failure after thiopentone administration, certain cardiovascular reflexes remain active to moderate its hypotensive effects.

Increase in the arterial blood pressure and atrial heart rate augument the tendency for dysrhythmia production during thiobarbiturate anaesthesia in dogs and mechanism responsible seems to be an imbalance between parasympathetic and sympathetic activity (Muir, 1977). Moreover, myocardial hypoxia consequential to arterial hypoxemia could be a contributory factor also (Rawlings and Kolata, 1983), in arrhythmia observed during ventilatory failure in the present study.

Hyperglycemia observed in these animals has been already discussed (see page No.78).

4. Mephentermine in circulatory insufficiency. (Group-II)

After lowering MAP to 27.9% of the 0 hr values by additional doses of thiopentone, mephentermine was given (0.5 mg/kg, i.v.) and observations were made for 60 min.

When hypotension is severe and prolonged due to thiopentone, vasoconstrictor drugs could be used to restore circulatory integrity (Dundee and Wyant, 1974-b). Moreover, it has been suggested by Steen and Michenfelder (1979) that if respiratory and circulatory supports are instituted early enough and adequately maintained, cerebral recovery is expected even when EEG activity is initially absent. Our findings do corroborate with theirs. Circulatory integrity had been restored and rise in arterial pressure was always followed by return of electrical activity in EEG and within 15 min after administration of mephentermine, the dilated pupils were constricted, suggesting reversal of cerebral hypoxia. Mephentermine also crosses the blood-brain barrier with ease and is supposed to be a mild cerebral stimulant with about half the activity of amphetamine (Vickers <u>et al</u>., 1978b; Williams, 1980).

Mephentermine has mixed direct and indirect action on autonomic nervous system. It possess alpha activity due to the release of norepinephrine stores in adrenergic nerve terminals, and beta activity due to a direct effect on receptors.

It causes a sustained pressor response. Mephentermine has a methyl substitution at the alpha carbon, therefore, it is not a good substrate for monoamine oxidase enzyme. The other important enzyme for disposition of the biogenic amines is catechol-o-methyl transferase which can act only on the catechols. Since, mephentermine is not a catechol, it is immune to catechol-o-methyl transferase. This explains its longer duration of action. The effects of mephentermine are controversial. Ogborn (1976) reported that pressor response is due to augumentation of myocardial contractility and cardiac output, instead of vasoconstriction. Similarly, in dogs Walsh et al. (1968) found striking elevation of ventricular function curve with little effect on peripheral vascular resistance. In some cases net vascular effect may be vasodilatation, which appears not to involve beta receptors (Caldwell and Goldberg, 1970). In dogs, anaesthetised with pentobarbitone and ventilating spontaneously, Lorsley and Eckstein (1961) found increase in cardiac output and arterial pressure with variable response i.e. increase or decrease in heart rate, right atrial pressure and calculated peripheral resistance. Contrary to all, Vickers et al. (1978-b) are of the opinion that, mephentermine causes increase in systemic vascular resistance with little changes in cardiac output. Results of our experiments reveal, a definite, immediate and sustained pressor response antagonising the circulatory insufficiency caused by excess doses of thiopentone. Keeping in view the arterial normotension, the close association

of heart rate with decreasing CVP, it can be said that the cardiac function had improved.

Mephentermine has been reported to have little direct effect on myocardial irritability (Hellerstein et al., 1952). In our experiments, ectopic beats were observed, but were transient and benign. All sympathomimetic amines in sufficient doses are capable of producing ectopic rhythms. Abolishing of III-degree AV.block in animal No.37M03 is itself suggestive of cardiac stimulatory effect of mephentermine.

There was a moderate increase in blood glucose for 30 min after mephentermine administration, which could be due to alterations in carbohydrate metabolism and this needs further investigation. Although mephentermine acts partly due to release of endogenous norepinephrine, same cannot be said to be responsible for this hyperglycemic effect in buffalo calves of the present study. This is so, because administration of norepinephrine in pressor doses, itself failed to elicit hyperglycemia (see results of group-III, page 42). Considerable species variation exists as far as hyperglycemic effect of norepinephrine is concerned. In horses, Anderson and Aitken (1977) reported marked hyperglycemia after norepinephrine infusion. They proposed that the glycogenolytic receptors in horse liver appear to be of alpha type, similar to man and rat, but unlike dog where such receptors are of beta type. Mephentermine also has a direct effect on beta adrenergic receptors, could it be the reason for hyperglycemia? In swine, Baetz et al. (1973)

did not find much increase in plasma glucose during norepinephrine infusion as compared to manyfold increase during epinephrine infusion and suggested that the sensitivity of liver, muscles and adipose tissue to norepinephrine is much less than in the man and sheep. This group also concluded that release of insulin from pancreas is blocked by both epinephrine and norepinephrine. What mechanism is involved in increasing blood glucose levels after mephentermine administration and keeping it relatively unaffected after norepinephrine infusion in buffaloes needs further study. One important consideration needs mention here, that effects of exogenous norepinephrine are in many situations different than that released endogenously, as exogenously administered norepinephrine may fail to reach the target site. Until more becomes clear about autonomic receptors, role of insulin and contrainsular hormones in carbohydrate metabolism in buffaloes, any explanation given would be more of conjecturing.

5. Norepinephrine in circulatory insufficiency.(Group-III)

In these experiments mean arterial pressure was reduced to 30% of the 0 hr value by additional doses of thiopentone. Such a degree of hypotension could quickly lead to the development of irreversible shock due to loss of regulation of vital processes from brain (Ferguson et al.,1978) unless pharmacological support to this

circulatory inefficiency is provided. Bagwell and Daniell (1970) and Vickers et al. (1978b) have suggested use of norepinephrine in the treatment of hypotension and opined that, close monitoring of cardiovascular function is imperative. Norepinephrine base given at the rate of 0.18±0.01 µg/kg/min caused about three fold increase in MAP in hypotensive buffalo calves. No sooner the arterial pressure started rising, electrical activity in the ECG reappeared suggesting its ability to ameliorate the depressed cerebral circulation indirectly. Results of the present study revealed, that this rate of administration of norepinephrine was sufficient to restore arterial pressure towards normalcy. Discontinuation of the drip did not reverse the already achieved beneficial effects indicating that continuous infusion for half an hour provides a stable and satisfactory improvement. Remarkable differences from mephentermine administration in similar situations (see group-II), were, relatively slower restoration in CVP and not a marked increase in HR.

It is well established that in normotension, norepinephrine infusion increases arterial pressure, peripheral vascular resistance, myocardial contractility and decreases heart rate (Goldenberg et al., 1950; Allwood et al, 1963; Adams, 1982). Subsequent to the norepinephrine infusion in normotensive horses and cattle, bradycardia is reported, which is proposed to be a vagal mediated reflex in response to elevation of blood pressure (Anderson and

Aitkin, 1977; Gregory and Watton,1981). For obvious reasons, we should not expect operation of vagal reflex as the already low MAP was elevated to just near normal limits only. In hypotensive dogs, norepinephrine did not change the heart rate (Bagwell and Daniell, 1970) and this corroborates with our findings. Bretz et al. (1973) concluded that pressor response of norepinephrine is primarily due to vasoconstriction. It has been emphasized by Klein and Sherman (1977) that most of studies of venous motor responses have shown that these vessels react to pressor amine administration by constricting. This would consequently increase venous return. Thus, it appears that venoconstriction along with enhanced myocardial contractility resulted in the elevation of arterial pressure during hypodynamic circulatory insufficiency in the present study too.

Anaesthetic-adrenergic cardiac arrhythmias are induced by beta adrenergic stimulation and are facilitated by increased heart rate, arterial pressure and by release of potassium from liver (Katz and Bigger, 1970). The tendency for catecholamines inducement of arrhythmias is further enhanced by use of thiobarbiturates (Claborn and Szabuniewicz, 1973; Szabuniewicz et al.,1975; Rezakhani et al., 1977). Norepinephrine administration is known to cause arrhythmias by activating the latent pacemaker cells (Bagwell and Daniell, 1970; Adams, 1982),

and this would explain more frequent and persistent arrhythmias observed in our study. Primary T-wave changes observed after the norepinephrine infusion have been also observed in cattle (Gregory and Wotton, 1981; Wielke and Klopzig, 1985).

Although both, mephentermine and norepinephrine were comparable in their ability to restore the circulatory status but former appears to be better, because of two basic reasons; one, a single dose of mephentermine produced sustained response contrary to norepinephrine drip which had to be continued and monitored for half an hour. Two, the myocardial irritability was more with norepinephrine.

6. Dexamethasone in circulatory insufficiency. (Group-IV)

Shock of differing etiology converges on a final common pathway of a reduction in cardiac output and tissue perfusion, associated with an intensive vasoconstrictive response in adrenergically sensitive splanchnic and cutaneous beds. Corticoid treatment of circulatory shock is established in horse and dog and is also indicated in other species (McDonald, 1982). Mechanisms by which glucocorticoids provide beneficial effects are not understood, but massive doses rather than physiological doses are required to be given. Several postulated mechanisms for the protective action of corticosteroids in shock have been proposed and may be classified as haemodynamic, metabolic and membrane-stabilising actions. Suggested protective

effects of corticosteroids on haemodynamics include; prevention of excessive vasoconstriction by acting directly on vascular smooth muscles (Lillehei et al., 1964; Altura et al., 1974) and by alpha adrenergic blockade (Dietman et al., 1970); improvement in cardiac output, arterial pressure and tissue blood flow (Ferguson et al., 1978). Metabolic effects include, induction of key enzymes in oxidative metabolism (Lefer and Verrier, 1970) and citric acid cycle (Schumer, 1974). Corticosteroids will prevent cell membrane damage and maintain membrane transport mechanisms near normal. This would consequently preclude the shifting of extracellular fluid into intracellular compartment (Grinstein-Nadler and Bottoms, 1978).

Observations of these five trials in our study, indicate that dexamethasone at the rate of 4 mg/kg given i.v. soon after circulatory insufficiency induced with excess of thiopentone had marked beneficial effects. Barbiturates when given excessively may injure capillary musculature directly (Booth, 1982a) and membrane stabilising action of dexamethasone (Grinstein-Nadler and Bottoms, 1978) in such circumstances would be beneficial.

Electrical activity in EEG reappeared only after there was an appreciable rise in MAP, probably within the limits of autoregulation, and with course of time reflexes also improved. Dexamethasone has been reported to increase blood flow to cerebral cortex and hypothalamus in dogs

made hypotensive by bleeding (Ferguson et al., 1978).

Increase in arterial pressure started 1.75±0.76 min after dexamethasone had been injected. Thus dexamethasone in massive doses had an immediate effect on arterial pressure, which is in agreement with the findings of other workers (Grinstein-Nadler and Bottoms, 1976; Ferguson et al., 1978). Thereafter, haemodynamic ligands remained in safe limits and before termination of the experiment, values were close to 0 hr values. An immediately increase by 160% and subsequently further improvement in arterial pressure with a progressive fall in CVP and relatively unaffected heart rate indicate inotropic action of dexamethasone. Positive inotropic effects of corticosteroids are established (Sambhi et al., 1966; Jenkins and Clark, 1977).

In one calf (No.71D01) serious and could be fatal arrhythmia developed 25 min after dexamethasone administration but sinus rhythm was established spontaneously. Thus, further substantiate the aforementioned cardiotropic and membrane stabilising effects of dexamethasone.

Unlike non-ruminants, ruminants are dependent on gluconeogenesis for their normal supply of glucose (Stevenson and Wilson, 1963). It is well known that cortisol increases conversion of aminoacids to glucose and inhibit peripheral glucose utilisation (McDonald, 1982). The immediate increase in blood glucose as observed

in our experiments, must be due to decreased glucose utilisation rather than gluconeogenesis, as it would take many hours.

From our findings, we can conclude that dexamethasone in massive doses should be a valuable adjunct to the therapy of circulatory insufficiency due to excessive doses of thiopentone.

7. Prothepaide in ventilatory failure. (Group-V)

The treatment of barbiturate overdose with analeptics remains controversial and it has been emphasised that under no circumstances should analeptics be used in the emergency treatment of acute respiratory failure with an apneic patient in immediate danger of death from hypoxia, instead artificial ventilation must be initiated without delay (White, 1971). Since it is not always possible for a clinician, especially involved in large animal practice in field conditions to apply modern resuscitative measures with oxygen equipment, a scope for analeptics still remains. This has led us to evaluate the efficacy of such a paradoxical approach. The therapeutic and prophylactic use of doxapram as an analeptic has been described (Dundee and Wyant, 1974b; Ross and Bremnock, 1981; Booth, 1982b).

Animals of groups-V, VI, VII and VIII received thiopentone in an otherwise fatal dose and all other aids to recovery from apnea, such as artificial ventilation, were deliberately denied in order to submit the drugs to

the more severe test. Thus, it was considered, that these experiments would impose much more severe conditions than are likely to be encountered during routine anaesthesia. Our experiments were not designed to advocate the use of these drugs in routine anaesthesia as a taken for granted alternative, but, could these drugs be of some value in extreme situations when other aids are not available. It is obvious that the most urgent and crucial requirement in apneic patient is restoration of the breathing and that is what prethcamide and nikethamide did.

Prethcamide is claimed to be a powerful respirotonic. It stimulates the respiratory center and increases minute volume by increasing tidal volume. There is slight and transient increase in pulse and blood pressure. Its use has been also indicated in respiratory arrest and barbiturate poisoning (Anonymous, 1984).

As indicated by EEG, the temporal effects were observed 1.6±0.28 min after its administration. Return of reflexes, response of animal to deep pin-pricks and EEG wave pattern are all suggestive of CNS excitation. It would also indicate that undue stimulation after prethcamide be avoided. Paraesthesia, muscular twitching and tremors can occur after prethcamide administration (Reynold, 1982).

The most important effect was return of ventilatory efforts as early as 2.6±0.47 min after its administration. It is so, because serious brain damage can occur between

4 to 6 min after total ventilatory failure (Paliah and Gordon, 1967). There was a marked improvement in the respiratory minute volume and effects were sustained. Arterial carbon dioxide tension which had increased during ventilatory failure was restored to normalcy indicating efficacy of ventilation. Arterial oxygen tension improved considerably, however, values remained lower than base values but were within safer limits. Decrease in arterial pO_2 without increase in pCO_2 is commonly seen with general anaesthesia and is attributed to increased ventilation perfusion inequalities (Peshin and Nigam, 1985).

Prethcamide acts directly on medullary centers (Atkinson et al., 1977) and respiratory rate is increased. Contrary to the claim of manufacturer, prethcamide in buffaloes improve ventilation primarily due to increase in rate.

Cardiovascular effects of prethcamide were seen only after cerebral and ventilatory effects were evident. Initial transient rise in arterial pressure can be attributed to generalised CNS excitation and probably extension of stimulation of medullary respiratory centers. With the course of time, the changes in cardiovascular parameters observed during ventilatory failure were ameliorated after ventilation was restored. This could be obviously because of elimination of the hypoxic and hypercapnic drives.

Changes in heart rate were undulatory in contrast to the effect on arterial pressure. There was an increase in the heart rate 15 min after prethcamide administration, this could be probably compensatory to hypotension, which in due course of time returned towards normalcy. Decrease in CVP at 15 min interval can be attributed to increase in the heart rate.

Arrhythmias observed were transient and it is generally known that analeptics cause cardiac arrhythmias (Rose and Breznock,1981).

It can be concluded from our study that in buffalo calves deeply anaesthetised with thiopentone, prethcamide causes general CNS excitation, increases respiratory rate and consequently respiratory minute volume. Therefore, when artificial means of ventilation are not available its use can be considered.

8. Nikethamide in ventilatory failure. (Group-VI)

As far as return of initial ventilatory effort is concerned, it was comparable with prethcamide, but restoration of regular rhythm took longer time. Doses of nikethamide as an analeptic, under such circumstances in buffaloes are much higher than, what were used for dogs by Cairy et al. (1961).

Resumption in electrical activity in ECG was seen along with reflex activity and took much longer time than prethcamide. Excitation of central nervous system was

also evident as nikethamide is known to stimulate both cerebral cortex and spinal cord (Booth,1982b) and has been proposed to enhance excitation rather than blocking inhibition.

Nikethamide administration in apneic calves increased minute volume and brought respiratory rate within 0 hr range. Contrary to prethcamide, it seems that respiratory minute volume is increased by augumenting tidal air rather than respiratory rate. Nikethamide acts directly on medullary respiratory centres as well as through carotid and aortic bodies (Atkinson et al.,1977). Thus it is possible to stimulate respiratory centers indirectly at a time when direct medullary stimulation of the centers would not be effective. Effectiveness of ventilation is explicit from near normal arterial oxygen and carbon dioxide tensions. Slower return of pCO_2 towards normaley than pO_2, could be due to the difference of these gases in the body stores (Marshall and Wyche, 1972).

Cardiovascular response to the injection of nikethamide was variable. Increase in heart rate was accompanied with increase in MAP in three calves, while in other two it remained relatively unaffected. Wang and Ward (1977) concluded that even large doses of the drug induced inconsistent effects on arterial pressure and the heart. Reports regarding cardiovascular effects of nikethamide are not congruent (Atkinson et al.,1977; Vickers et al., 1978a; Booth, 1982b).

After 30 min of nikethamide administration, mild hypotension prevailed. Hypotension and cardiac arrhythmias, as observed in the present study, are among the harmful side effects of analeptics (Ross and Bremnock,1961).

One calf died 70 min after nikethamide administration due to respiratory arrest, probably due to failure of medullary respiratory center itself. Such a possibility has been suggested by Vickers et al. (1978a) while discussing nikethamide.

9. Mephentermine and prethcamide in circulatory insufficiency with ventilatory failure. (Group-VII)

Mephentermine as a circulatory support and prethcamide as a ventilatory support were evaluated in thiopentone induced circulatory insufficiency (Group-II) and ventilatory failure (Group-V) respectively. Results were encouraging and in this group both drugs were used for sole pharmacological circulatory and ventilatory support. Outcome of the experiments in general was predictable i.e. general CNS excitation, augumentation of respiratory rate and consequently increased minute volume, tachycardia, restoration of MAP and CVP to normalcy. Careful perusal of the data revealed that cardiovascular stimulating responses were more prominent than when mephentermine or prethcamide was given alone. At 5 min after administration of both mephentermine and prethcamide, the heart rate and MAP were remarkably high and CVP was lower than 0 hr value.

Subsequently, there was moderation with time, in these parameters. But tachycardia persisted till termination of the study. Arterial pressure also remained above 0 hr value for 30 min. This would indicate that while using these drugs in combination under true clinical situations, doses can be reduced.

One unpredictable but desirable response of the combination was the absence of any kind of serious arrhythmia.

10. Norepinephrine and nikethamide in circulatory insufficiency with ventilatory failure. (Group-VIII)

Norepinephrine infusion and nikethamide could restore cardiovascular and ventilatory functions in four calves. Results of the combination were mostly predictable when compared with calves where these drugs were used alone, either for circulatory insufficiency or for ventilatory failure.

There was early restoration of ventilation in this group as compared to when nikethamide was given alone. Norepinephrine itself has some respiratonic effects (Goldenberg et al., 1960). In one animal nikethamide failed to establish regular ventilatory efforts irrespective of the fact that it could produce pressor response.

Stability in arterial pressure was brought earlier when norepinephrine drip was followed by nikethamide. Except initial tachycardia, the heart rate remained within

limits, although, after disconnecting the norepinephrine drip, there was a mild increase in heart rate. It appears to be a compensatory effort in response to decrease in arterial pressure. Norepinephrine when given alone did not cause a significant fall in MAP after weaning the drip, but nikethamide alone did cause a significant hypotension at comparable time. Vickers et al. (1978a) proposed that nikethamide may cause myocardial depression.

Results of these experiments suggest that if choice is to be made between mephentermine plus prethamide and norepinephrine plus nikethamide when former combination should be preferred.

SUMMARY AND CONCLUSIONS

Present study was undertaken to evaluate the effects of certain drugs on circulatory insufficiency and ventilatory failure induced with excess doses of thiopentone sodium. Studies were done on 40 apparently healthy male buffalo calves (Bubalus bubalis) of one and a half to two years and weighing between 55 to 120 kg. The animals were divided in eight groups of five each. In four groups circulatory insufficiency was induced by giving thiopentone sodium in excessive doses. Ventilation was controlled mechanically and following treatment given:-

Group-I; - No drug was given and served as control and monitored up to 75 min.

Group-II; - Mephentermine sulphate was given at the rate of 0.5 mg/kg and monitored for 60 min.

Group-III; - Norepinephrine drip (4 µg/ml) was given up to 30 min and monitored for 60 min.

Group-IV;- Dexamethasone sodium phosphate was given at the rate of 4 mg/kg and monitored for 75 min.

In other two groups ventilatory failure was induced by additional increments of thiopentone sodium. Mechanical support to ventilation was not provided, instead following analeptics were evaluated:-

Group-V; - Prethcamide was given at the rate of 9 mg/kg and monitored for 45 min.

Group-VI; Nikethamide (25%) was given in increments over a period of 6.75±1.03 (mean ± standard error) until the regular ventilatory efforts were established. Animals were subsequently monitored for 75 min.

In the remaining two groups, circulatory insufficiency and ventilatory failure was induced with thiopentone and was treated only by combination of drugs. No mechanical ventilatory support was provided at any stage.

Group-VII; Mephentermine was given at the rate of 0.5 mg/kg, followed by prethamide at the rate of 9 mg/kg and monitored for 75 min.

Group-VIII; Norepinephrine drip was started as described for group-III. This was followed by nikethamide administration in incremental doses until regular ventilatory efforts were restored. Animals were subsequently monitored for 75 min.

All drugs were administered through the ear vein.

Following parameters were monitored using standard techniques:

Arterial pressure (systolic, diastolic and mean), central venous pressure (CVP), electrocardiogram (ECG), electroencephalogram (EEG), various reflexes, rectal temperature and blood gases. Periodical venous blood samples were also collected for determination of blood haemoglobin, blood glucose, plasma total proteins and plasma creatinine. In animals of group-V, VI, VII

and VIII respiratory rate and respiratory minute volume was also monitored.

Stable fall in mean arterial pressure (MAP) to 6.45±0.811 kPa (48.9±1.89 mmHg) and a flat ECG were considered to indicate an acute thiopentone overdosage with circulatory insufficiency. While complete cessation of any visible ventilatory efforts was considered to indicate ventilatory failure. Results indicated that the difference between the dose of thiopentone for inducing ventilatory failure and circulatory insufficiency was narrow.

Characteristic features of circulatory inefficiency were fall in MAP to 30% of the base value, slight increase in heart rate (HR), marked elevation of CVP, increase in capillary refill time, absence of reflexes and no evidence of electrical activity in ECG. The characteristic features of ventilatory failure included no evidence of air flow through the endotracheal tube, marked arterial hyperapnia and hypoxemia, decrease in venous oxygen tension, initial hypotension followed by tachycardia with normotension. Blood glucose levels also increased.

Out of five calves from group-I, where circulatory support was not provided, one died due to acute myocardial depression. The other two calves died due to respiratory failure, when after 75 min the positive pressure ventilator was weaned.

In group-II, where mephentermine was administered, circulatory functions were restored within 5 min. Electrical activity in EEG and reflex activity also returned subsequently.

Norepinephrine infusion at the rate of 0.19 ±0.01 µg/kg/min in saline for 30 min was sufficient to provide satisfactory improvement in cardiovascular function. Frequent and persistent arrhythmias were observed as compared to group-II.

Dexamethasone sodium phosphate when given soon after circulatory insufficiency, induced with thiopentone sodium, had marked beneficial effects. The arterial pressure and CVP was brought to normal within 45 min without significantly changing the heart rate. Blood glucose levels remained elevated for 45 min.

Prethamide (9 mg/kg) given intravenously soon after thiopentone induced ventilatory failure restored the respiratory minute volume. Effects started 2.6±0.47 min and full regular respiration ensued within 10 min after its administration. Respiratory rate remained elevated for 45 min. Blood gases returned to normal limits within 15 min. Transient hypertension followed by hypotension, and arrhythmias were also observed. General central nervous system (CNS) excitation was a characteristic feature.

When nikethamide was given at the rate of 95 mg/kg in incremental doses, four calves survived. Ventilatory

efforts were initiated 2.75±0.87 min after its administration and full regular respirations ensued within 10 min. Respiratory rate remained generally within normal limits but there was a marked increase in respiratory minute volume. The initial cardiovascular responses were almost similar to prethcamide but after 30 min of nikethamide administration, hypotension was observed. Arrhythmias were also recorded in three animals. General CNS excitation was present.

When mephentermine sulphate and prethcamide was used to correct both circulatory insufficiency and ventilatory failure, results were encouraging. All calves survived. Findings were predictable i.e. general CNS excitation, increased respiratory rate and consequently increased minute volume, tachycardia, restoration of MAP and CVP levels towards normalcy. No conduction abnormalities were recorded in these five animals after administration of both the drugs.

Out of five animals from group-VIII where, norepinephrine drip and nikethamide in incremental doses was given, only four survived. Regular ventilatory efforts could not be established in one animal which died. The results were relatively predictable when compared with animals (Group-III & VI) where these drugs were given singly. Unlike mephentermine plus prethcamide, this combination had late hypotensive effects when the drip was weaned.

Plasma creatinine, plasma total proteins, and blood haemoglobin was not affected in any animal during the course of entire study.

From the present experiments following conclusions can be drawn:-

1- When thiopentone is given in excessive doses, in buffaloes, the major effect, apart from ventilatory failure is acute myocardial depression.

2- Mephentermine appears to control the thiopentone induced circulatory insufficiency, effectively, and effects are sustained.

3- Prethcamide appears to cause stimulation of thiopentone induced depression of central nervous system and ventilatory failure.

4- Mephentermine and prethcamide appears to be a relatively suitable combination to control circulatory insufficiency and ventilatory failure due to excessive thiopentone administration. Oxygen therapy should provide additional beneficial effects. Moreover in an emergency, when artificial means of ventilation are not available, use of this combination can be considered.

5- Results of the present study suggest that dexamethasone should be a valuable adjunct to therapy of circulatory insufficiency in buffaloes.

LITERATURE CITED

Adams, H.R. 1982. Adrenergic and Antiadrenergic Drugs. In: Veterinary Pharmacology and Therapeutics, Eds. Booth, N.H. and McDonald, L.E. 5th Ed. pp.88-112. The Iowa State University Press, Ames, Iowa, 50010, USA.

Allwood, M.J., Cobbold, A.F. and Ginsburg, J. 1963. Peripheral vascular effects of noradrenaline, isoprophylnoradrenaline and dopamine. Br.Med.Bull. 19: 132-136.

Altura, B.M., Altura, B.T. and Lemsbey, S.C. 1974. Pharmacodynamic actions of corticosteroids on the microcirculation and vascular somooth muscle. In: Steroids and Shock Edt. T.M.Glenn. pp.67-88. University Park Press, Baltimore, Md.

Anderson, D.P., Allen, W.J., Bareroft, H., Edholm, O.G. and Manning, G.W. 1946. Circulatory changes during fainting and coma caused by oxygen lack. J.Physiol. (London). 104: 428-436.

Anderson, M.C. and Aitken, M.M. 1977. Biochemical and physiological effects of catecholamine administration in the horse. Res.vet.Sci. 22: 357-360.

Anonymous 1984. "Restimulen" Literature provided with the packing. Batch No.4J222. S.C.Pharmaceuticals Ranoli, Distt. Baroda, India.

Atkinson, R.S., Rushman, G.B. and Lee, A.L. 1977. A Synopsis of Anaesthesia. 8th Ed. pp.486-503. John Wright & Sons Ltd. Bristol.

Baetz, A.L., Witzel, D.A. and Graham, C.K. 1973. Certain metabolic responses of swine to epinephrine and norepinephrine infusion. Am.J.Vet.Res. 34: 497-500.

Bagwell, E.E. and Daniell, H.B. 1970. Comparative effects of dopamine and norepinephrine on myocardial experimental cardiogenic shock. J.Pharmacol.Exp.Ther. 173: 357-363.

Bell, G.H., Smith-Kinlie, D. and Paterson, C.R. 1980. Text book of physiology 10th Ed. pp.289-295. Churchill Livingstone Longman Group Ltd. Robert Stevenson House, 1-3, Baxter's Place, Leith Walk Edinburgh.

Booth, N.H. 1982-a. Intravenous and other Parenteral Anaesthetics. In: Veterinary Pharmacology and Therapeutics. Eds. Booth, N.H. and McDonald, L.E. 5th Ed. pp.203-254. The Iowa State University Press. Ames, Iowa, 50010, U.S.A.

Booth, N.H. 1982-b. Stimulants. In: Veterinary Pharmacology and Therapeutics. Eds. Booth, N.H. and McDonald, L.E. 5th Ed. pp.346-352. The Iowa State University Press, Ames, Iowa. 50010, USA.

Brooker, M.M., French, D.M. and Molano, P.A. 1949. Further observations on the effect of prolonged thiopental (pentothal) anesthesia on metabolism of carbohydrates and proteins in dogs. J.Pharmacol. 96: 145-150.

Brooker, M.M., Maloney, A.H., Tureman, J.H. and Rateliff, C. 1952. Some metabolic factors influencing the course of thiopental anesthesia in dogs. Am.J.Physiology. 170: 168-172.

Cairy, C.F., Leash Aaron and Sisodia, C.S. 1981. Comparison of several drugs in treating acute barbiturate depression. J.Am.Vet.Med.Assoc. 138: 129-131.

Caldwell, N.W. and Goldberg, L.I. 1970. An evaluation of the vasodilation produced by mephentermine and certain other sympathomimetic amines. J.Pharmacol.Exp.Ther. 172: 297-309.

Carey, L.C., Lowery, B.D. and Cloutier, C.T. 1970. Blood sugar and insulin response of humans in shock. Ann. Surg. 172: 342-347.

Claborn, L.D. and Sabuniewicz, M. 1973. Prevention of chloroform and thiobarbiturate cardiac sensitization to catecholamines in dogs. Am.J.Vet.Res. 34: 801-804.

Clark, D.R. 1977. Recognition and treatment of cardiac emergencies. J.Am.Vet.Med.Assoc. 171: 98-106.

Clowes, G.H.A.Jr., O'Donnel, T.F.Jr., Ryan, N.T. and Blackburn, G.L. 1974. Energy metabolism in sepsis; treatment based on different patterns in shock and high output stage. Ann.Surg. 179: 684-696.

Cryer, P.E., Coran, A.G., Sode, J., Lerman, C.M. and Horwitz, D.L. 1972. Lethal Escherichia coli septicemia in baboon; alpha adrenergic inhibition of insulin secretion and its relationship to the duration of survival. J.Lab. Clin.Med. 79: 622.

Daly, M.B. and Scott, M.J. 1958. The effects of stimulation of the carotid body chemoreceptors on heart rate in the dog. J.Physiol. (London) 144: 148-166.

Dietzman, R.H., Hotsay, C.J. and Lillehei, R.C. 1970. Drugs in the Treatment of Shock. In: Pharmacology for Physicians. 4th Ed. pp.1-5. W.B.Saunders, Co. Philadelphia.

Dundee, J.W. and Todd, U. 1958. Clinical significance of the effects of thiopentone and adjuvant drugs on blood sugar and glucose tolerance. Br.J.Anaesth. 30: 77-82.

Dundee, J.W. and Wyant, G.M. 1974. Intravenous Anaesthesia. 1st Ed. pp.64-127(a), 128-161(b). Churchill Livingstone (Longman Group Ltd.), 23 Ravelston Terrace, Edinburgh.

Edwards, W.S. 1951. The effects of lung inflation and epinephrine on pulmonary vascular resistance. Am.J. Physiol. 167: 756-762.

Ferguson, J.L., Roesel, O.F. and Bottoms, G.D. 1978. Dexamethasone treatment during hemorrhagic shock: blood pressure, tissue perfusion, and plasma enzymes. Am.J.Vet.Res. 39: 817-824.

Filmore, S.J., Shapiro, M. and Killip, T. 1970. Serial blood gas studies during cardiopulmonary resuscitation. Ann.Intern.Med. 72: 465-469.

Flynn, J.T., O'Grady, O.E., Herrera, J., Kushner, B.J., Cantolino, S. and Milam, W. 1977. Retrolental fibroplasia. I. Clinical observations. Arch.Ophthalmol. 95: 217-223.

Folin, O. and Wu, H. 1919. J.Biol.Chem. 38: 81. (Cited by B.L.Oser. In: Hawk's Physiological Chemistry. 14th Ed; pp.1040-1043, McGraw Hill, New York).

Folin, O. and Wu, H. 1920. J.Biol.Chem. 41: 367. (Cited by B.L.Oser. In: Hawk's Physiological Chemistry. 14th Ed; pp.1062-1063. McGraw Hill, New York).

Frank, M., Maynard, D.E., Tsanaclis, L.M., Major, E. and Coutinho, P.E. 1984. Changes in cerebral electrical activity measured by the cerebral function analysing monitor following bolus injections of thiopentone. Br.J.Anaesth. 56: 1075-1081.

Gillespie, J.R., Tyler, W.S. and Hall, L.W. 1969. Cardiopulmonary dysfunction in anesthetized laterally recumbent horses. Am.J.Vet.Res. 30: 61-72.

Gilroy, B.A., Rockoff, M.J., Dunlop, B.J. and Shapiro, H.M. 1980. Cardiopulmonary resuscitation in the nonhuman primate. J.Am.Vet.Med.Assoc. 117: 867-869.

Goldenberg,M., Aranow,H.Jr., Smith,A.A. and Faber,M. 1950. Pheochromocytoma and essential hypertensive vascular disease. Arch.Intern.Med. 86: 823-836.

Gopakumar,N. 1977. Pharmacological and biochemical effects of some autonomic drugs affecting sympathetic system in buffalo calves. Ph.D. Dissertation. Punjab Agricultural University, Ludhiana.

Gregory,N.G. and Wotton,S.B. 1981. Studies on the sympathetic nervous system: T-wave vectorcardiogram in cattle. Res.vet.Sci. 30: 75-78.

Grinstein-Nadler,E. and Bottoms,G.D. 1976. Dexamethasone treatment during hemorrhagic shock: Changes in extracellular fluid volume and cell membrane transport. Am.J.Vet.Res. 37: 1337-1343.

Hamlin,R.L., Redding,R.W., Reiger,J.E., Smith,R.C. and Fryrn,R.E. 1965. Insignificance of the "Glucose effect" in dogs anesthetized with pentobarbital. J.Am.Vet.Med.Assoc. 146: 238-241.

Harrison,L.C., Martin,F.I.R. and Melick,R.A. 1976. Correlation between insulin receptor binding in isolated fat cells and insulin sensitivity in these human subjects. J. Clin.Invest. 58: 1435-1441.

Hellerstein,H.K., Brofman,B.L. and Caskey,W.H. 1952. Shock accompanying myocardial infarction: treatment with pressor amines. Am.Heart J. 44: 407-427.

Horsley,A.W. and Eckstein,J.W. 1961. Hemodynamic responses to administration of mephentermine in normotensive and hypotensive dogs. Am.Heart. J. 61: 88-92.

Hrubetz,M.C. and Blackberg,S.N. 1938. Influence of nembutal pentothal, seconal, amytal, pentobarbital and chloroform on blood sugar concentration and carbohydrate mobilisation. Am.J.Physiology. 122: 759-764.

Jenkins, W.L. and Clark, D.H. 1977. A review of drugs affecting the heart. J.Am.Vet.Med.Assoc. 171: 85-92.

Johnson, S.H. 1949. The mechanism of hyperglycemia during anesthesia. An experimental study. Anesthesiology. 10: 378.

Katz, R.L. and Bigger, J.T.Jr. 1970. Cardiac arrhythmias during anesthesia and operation. Anesthesiology. 33: 193-213.

Klein, L. and Sherman, J. 1977. Effects of preanesthetic medication, anesthesia and position of recumbency on central venous pressure in horses. J.Am.Vet.Med.Assoc. 170: 216-219.

Kraaney, J.A. and Koehler, R.C. 1977. Influence of arterial hypoxia on cardiac and coronary dynamics in the conscious sinoaortic denervated dog. J.Appl.Physiol. 43: 1012-1018.

Kumar, N.G. and Bahga, H.S. 1976. Epinephrine and carbachol induced changes in blood picture and plasma electrolytes in Bubalus bubalis. Indian J.Anim.Sci. 46: 109-113.

Lafferty, J.J., Keykhah, M.M., Shapiro, H.M., Vanhorn, K. and Behar, M.G. 1978. Cerebral hypometabolism obtained with deep pentobarbital anesthesia and hypothermia (30C). Anesthesiology. 49: 159-164.

Lappas, D.G., John Powell, W.M. and Daggett, W.M. 1977. Cardiac dysfunction in the perioperative period: pathophysiology, diagnosis and treatment. Anesthesiology. 47: 117-137.

Lefer, A.M. and Verrier, R.L. 1970. Role of corticosteroids in the treatment of circulatory collapse states. Clin. Pharmacol.Ther. 11: 630-655.

Lillehei, R.C., Longerbeam, J.K., Block, J.H. and Manax, W.G. 1964. The nature of irreversible shock. Experimental and clinical observations. Ann.Surg. 160: 682-710.

Lecchesi,B.R. 1977. Antiarrhythmic drugs (and) inotropic agents and drugs used to support the failing heart. In: Cardiovascular Pharmacology. Ed. Antonaccio,M.J., Raven Press Books, Ltd., New York. USA.

Lucke,J.N. and Waterman,A. 1977. A portable resuscitation box for use in anaesthetic emergencies. J.Small Anim. Pract. 18: 423-428.

Marshall,B.E. and Wyche,M.L. 1972. Hypoxemia during and after anesthesia. Anesthesiology. 37: 178-209.

McDonald,L.E. 1982. Hormones Influencing Metabolism. In: Veterinary Pharmacology and Therapeutics. Eds. Booth,N.H. and McDonald,L.E. 5th Ed. pp.553-592. The Iowa State University Press, Ames, Iowa, 50010, U.S.A.

McDowall,D.G. 1980. Cerebral Blood Flow. In: General Anaesthesia Eds. Gray,T.C., Nunn,J.F. and Utting,J.E. 4th Ed., Vol.I pp.657-684. Butterworth & Co (Publishers) Ltd. 88-Kingsway, WC2B6AB, London (UK).

Mielke,H. and Klopzig,U. 1985. Electrocardiographic testing of cattle for dependence of cardiac action on adrenaline and noradrenaline, without and with vagolysis (Atropine) and beta-receptor blockade (propranolol) Arch.Exper. Vet.Med.Leipzig. 39: 193-206.

Mirakhur,K.K., Singh,J., Sharma,S.N. and Kohli,R.N. 1980. Effects of chloral hydrate and its combination with thiopental sodium in buffalo calves. Zbl.Vet.Med. A. 27: 708-716.

Mirakhur,K.K., Sobti,V.K. and Nigam,J.M. 1982. Effect of thiopentone anaesthesia on plasma catecholamines and cortisol in buffalo calves (Bubalus bubalis). Indian J.Vet.Surg. 3: 86-88.

Moffitt, E.A., Tarhan Sait, Lundberg, R.O. 1968. Anesthesia for cardiac surgery: principles and practice. Anesthesiology. 29: 1181-1205.

Moran, N.C. 1970. Evaluation of the pharmacologic basis for the therapy of circulatory shock. Am.J.Cardiol. 26: 570-577.

Morgan, B.C., Martin, W.E., Hornbein, T.F., Crawford, E.W. and Guntheroth, W.G. 1966. Hemodynamic effects of intermittent positive pressure respiration. Anesthesiology. 27: 584-590.

Muir, W.W. 1977. Thiobarbiturate induced dysrhythmias: The role of heart rate and autonomic imbalance. Am.J. Vet.Res. 38: 1377-1381.

Ndiritu, C. and Enos, R.L. 1977. Adverse reactions to drugs in a veterinary hospital. J.Am.Vet.Med.Assoc. 171: 335-339.

Nigam, J.M., Singh, J., Peshin, P.K. and Singh, A.P. 1983. Effects of chloral hydrate and thiopental sodium on haemodynamics, acid-base and blood gases in buffalo calves. Indian J.Vet.Surg. 4(2): 40-45.

Nunn, J.F. 1977. Applied Respiratory Physiology. 2nd Ed. pp.375-444. Butterworth & Co. (Publishers) Ltd. 88-Kingsway, WC2B6AB, London.

Ogborn, P. 1975. The role of vasoactive agent in shock therapy. Vet.Clin.North.Am. 6: 287.

Pulich, W.E. and Gordon, A.S. 1967. Cardiopulmonary resuscitation of dogs: Principles and Practice. J.Am.Vet.Med.Assoc. 151: 1719-1732.

Peshin, P.K., Krishnamurthy, D., Singh, K., Narasimi, M.N. and Nigam, J.M. 1986. Hemodynamic and blood gas changes in buffaloes (Bubalus bubalis) in the supine position following thiopentone anaesthesia with premedication. Vet. Res. Commun. (In press).

Peshin, P.K., Kulkarni, B.S., Singh, J. and Singh, A.P. 1983. Hemodynamic and ventilatory effects of experimental hypercapnia in buffalo calves. Paper presented in 7th Annual Symposium and Conference of the Indian Society for Veterinary Surgery held at Kerala Agricultural University, Mannuthy, Trichur, Kerala, India.

Peshin, P.K. and Nigam, J.M. 1985. Anaesthetic Management. In: Monograph on Diaphragmatic Hernia in Bovines. Eds. Krishnamurthy, D., Nigam, J.M., Peshin, P.K., Sharma, D.N. and Tyagi, R.P.S. pp.99-114. Haryana Agricultural University, Hisar, India.

Peshin, P.K., Nigam, J.M. and Mirakhur, K.K. 1985. Cardiovascular and respiratory changes in sheep during thiopentone and halothane anaesthesia. Indian J. Anim. Sci. 55: 91-97.

Peshin, P.K., Singh, A.P., Singh, J. and Nigam, J.M. 1982. Effect of xylazine (Rompun) on acid base balance and blood gases of the intestine, kidney and brain in calves. Acta Veterinaria (Beograd). 32: 123-130.

Phillips, R.A. and Freeman, N.E. 1933. Ether hyperglycemia. Proc. Soc. Expt. Biol. and Med. 31: 286.

Pierce, E.C. Jr., Lambertsen, C.J., Deutsch, S., Chase, P.E., Linde, H.W., Drippe, N.D. and Price, H.L. 1962. Cerebral circulation and metabolism during thiopental anaesthesia and hyperventilation in man. J. Clin. Invest. 41: 1664-1671.

Price,H.L. 1971. The Pharmacodynamics of Thiobarbiturates. In: Text Book of Veterinary Anesthesia. Edt. Soma,L.R. pp.105-110. The Williams and Wilkins Company, 428E Preston Street, Baltimore, Md. 21202, USA.

Price,H.L., Conner,E.H., Elder,J.D. and Dripps,R.D. 1952. Effect of sodium thiopental on circulatory response to positive pressure inflation of lung. J.Appl.Physiol. 4: 629-635.

Rawlings,C.A. and Kolata,R.J. 1983. Cardiopulmonary effects of thiopentone/lidocaine combination during anesthetic induction in the dog. Am.J.Vet.Res. 44: 144-148.

Reynolds,J.E.F. 1982. Pretomamide. 'Martindale' The Extra-Pharmacopia 28th Ed. pp.388. The Pharmaceutical Press, London.

Remakhani,A., Edjtehadi,M. and Sambuniewicz,M. 1977. Prevention of thiopental and thiopental/halothane cardiac sensitization to epinephrine in the sheep. Can.J. Comp.Med. 41: 389-395.

Ross,J.N. and Bremnock,E.M. 1981. Resuscitation. In: Veterinary Critical Care. Eds. Sattler,F.P., Knowles,R.P. and Whittick,W.G. pp.435-466. Lea and Febiger, Philadelphia, U.S.A.

Sambhi,M.P., Weil,W.B. and Udhoji,V.N. 1965. Acute pharmacodynamic effects of glucocorticoids. Circulation. 31: 823-830.

Schumer,W. 1974. The cellular metabolic approach to shock research and therapeutics. Circ.Shock. 1: 83-86.

Seehzer,P.H., Egbert,L.D., Linde,H.W., Cooper,D.Y., Dripps, R.D. and Price,H.L. 1960. Effect of CO_2 inhalation on arterial pressure, ECO_2 and plasma catecholamines and 17-OH corticosteroids in normal man. J.Appl. Physiol. 15: 454-458.

Short,C.E., Keats,A.S., Liotta,D. and Hall,C.W. 1968. Anesthesia for cardiac surgery in calves. Am.J. Vet.Res. 29: 2287-2294.

Singh,J., Mirakhur,K.K., Sobti,V.K. and Kohli,R.N. 1980. Haemodynamics, blood gas and metabolic alterations during thiopental anaesthesia in buffaloes. Zbl.Vet.Med. A: 27: 730-739.

Singh,J., Singh,A.P. and Peshin,P.K. 1985. Systemic and organ effects of thiopental sodium on oxygen environment and acid base status of calves. Indian J.Anim.Sci.55: 410-414.

Smith,H.C. and Hamlin,R.L. 1977. Regulation of the heart and blood vessels. In: Dukes' Physiology of Domestic Animals. Edt. Swenson,M.J. 9th Ed. pp.102-120. Comstock Publishing Associates, a division of Cornell University Press Ltd., Ely House, 37 Dover Street, London.

Sobti,V.K., Mirakhur,K.K., Krishnamurthy,D. and Nigam,J.M. 1982. Experimental studies on haemodynamics of haemorrhagic shock in buffalo calves. Indian J. Anim.Sci. 52: 391-395.

Soman,V. and Felig,P. 1977. Glucagon and insulin binding to liver membranes in a partially nephrectomized uremic rat model. J.Cli.Invest. 60: 224-232.

Steen,P.A. and Michenfelder,J.D. 1979. Neurotoxicity of Anesthetics. Anesthesiology. 50: 438-453.

Stevenson,D.E. and Wilson,A.A. 1963. Metabolic Disorders of Domestic Animals. pp.87-124. Blackwell Scientific Publications. Oxford.U.K.

Szabuniewicz, M., Davis,R.H.Jr. and Wiersig,D.O. 1975. Prevention of methoxyflurane and thiobarbiturate sensitization to catecholamines in dogs. Vet.Med. Small Anim.Clin. 47: 12-14.

Thomas,W.J., Cole,P.V., Hetherington,N.J., Prior,P.F. and Stefansson,S.B. 1985. Electrical activity of cerebral cortex during induced hypotension in man. A comparison of sodium nitroprusside and trimetaphan. Br.J. Anaesth. 57: 337.

Tyagi,R.P.S., Arnold,J.P., Usenik,E.A. and Fletchers,T.F. 1984. Effects of thiopental sodium (Pentothal sodium) anesthesia on the horse. Cornell Veterinarian LIV (4), 584-602.

Vickers,M.D., Wood-Smith,F.G. and Stewart,H.C. 1978. Drugs in Anaesthetic Practice-5th Ed.pp.337-417,(b) 241-252,(a) Butterworth & Co. (Publishers) Ltd. 88-Kingsway, WC2B6AB, London (UK).

Wang,S.C. and Ward,J.W. 1977. Analeptics. Pharmacol. Ther.(B) 3: 123-165.

Welch,G.H., Braunwald Eugene, Case,R.B. and Sarnoff,S.J. 1956. The effect of mephentermine sulfate on myocardial oxygen consumption, myocardial efficiency and peripheral vascular resistance. Am.J.Med. 24: 871-881.

White,R.J. 1971. Respiratory failure and resuscitation. In: Text book of Veterinary Anesthesia. Edit. Soman, L.R. 1st Ed. pp.510-528. The Williams and Wilkins Company, 428-E, Preston Street, Baltimore Md. 21202, USA.

Williams,N.E. 1980. Autonomic Drugs: In: General Anaesthesia Eds. Gray,T.C., Nunn,J.F. and Utting, J.E. 4th Ed. Vol.I pp.743-760. Butterworth & Co. (Publishers) Ltd. 88-Kingsway,WC2B6AB, London (UK).