A COMPARISON OF VANILLIC ACID DIETHYLAMIDE AND PENTYLENETETRAZOL AS AROUSAL AGENTS IN THE EQUINE SPECIES

by

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INTRODUCTION

The need for an effective arousal or analeptic agent for use in the equine species has been generally recognized; particularly so because of the variable response to intravenous anesthetics which occurs in this species. This variation in response has been variously attributed to the metabolic rate, existing disease or diseases, concentration and/or rate of administration of the anesthetic agent, tolerance to the anesthetic, concurrent administration of other drugs, idiosyncrasies and hemorrhage. It should be standard procedure to have an arousal and analeptic agent available with which to lighten the level or depth of anesthesia should respiratory embarrassment or extreme depression occur thereby allowing the surgeon to continue with the surgical procedure knowing that some of the hazards from the anesthesia have been controlled.

It is often desirable to shorten the recovery time following general anesthesia. Agents having this quality could be administered upon completion of surgery resulting in the horse attaining a standing position within a few minutes, then walking to his stall to further recover from the anesthetic. Many hours have been spent attending and restraining a horse during its recovery from various intravenous anesthetics. Only attendants which are qualified and experienced in handling horses recovering from anesthesia should be utilized in order to prevent injury to the horse or to the attendant. These are special problems which confront the veterinary surgeon. Many veterinarians avoid general anesthetics in the horse because of the long and often unpredictable periods of recovery.

Intravenous anesthetics are most commonly used for general anesthesia because of the ease of administration, relative low cost of equipment needed,

and the minimal requirement for professional assistants to maintain anesthesia. However, practicing veterinarians often hesitate to use general anesthesia due to their lack of confidence in the anesthetic agents and the prolonged and often unpredictable recovery period necessitating an experienced person to attend the animal during this period.

If an agent were available to eliminate the latter grievance by shortening the animal's recovery period, more surgery would be attempted which today seems too formidable to many veterinary surgeons.

The purpose of this investigation was to evaluate vanillic acid diethylamide[1] (VAD) and pentylenetetrazol[2] for use as such arousal agents in the horse following intravenous anesthesia.

REVIEW OF LITERATURE

Chloral Hydrate

As reported by Gilmour (1934), Flourens was the first to use general anesthetics in animals in 1847. Flourens utilized chloroform to anesthetize animals. Sollman (1948) reported that the first fundamental scientific work on anesthetics was published by Snow in 1858.

Chloral hydrate was first made by Liebig in 1832. In 1869, Liebrich utilized chloral hydrate as an anesthetic agent on the assumption that it would be converted to chloroform in the organism, as it is by alkalies in the test tube. The theory was later disproved; the blood and expired air contain no chloroform or, at most, insignificant traces.

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[1] "Emivan"; U. S. Vitamin and Pharmaceutical Corporation, New York, New York.
[2] "Metrazol"; Knoll Pharmaceutical Company, Orange, New Jersey.

Ore (1872-3), after making preparatory tests in dogs, produced anesthesia in man by the intravenous injection of chloral hydrate. There were several fatalities, however, and by 1877 the method had been discarded in man. Wright (1952) stated that Humbert is credited with the trial of this agent in horses. Nocard (1886, as reported by Wright) reported that he had used a 33 per cent aqueous solution of chloral hydrate intravenously. He utilized this solution in the horse, ox, and dog. He also reported that in 500 to 600 injections he had had no anesthetic deaths.

Chloral hydrate is excreted in the urine in 1-1/2 to 18 hours as the non-toxic trichlorethyl glucuronic acid (Merring, 1881 as taken from Sollman, 1948). It is postulated that chloral hydrate is converted in the body to trichlorethyl alcohol which is then conjugated in the liver with glucuronic acid, forming trichlorethyl glucuronic acid which is eliminated through the kidneys (Payne, 1954).

Tolerance to chloral hydrate is due to increased capacity of the liver to conjugate chloral hydrate (Mitzescu, 1930 as reported by Sollman).

A study conducted on mice by Mackay and Cooper (1962) at Yale University indicated that chloral hydrate is in itself a potent hypnotic, but of short duration, and that its action is limited by a rapid reduction to trichlorethanol with the later compound continuing the hypnotic activity. The level of chloral hydrate and trichloroethanol in the brain was correlated with the degree of hypnosis.

Goffinet (1939) observed that chloral hydrate was the best anesthetic for the equine species. He based this observation on the basis of no excitement, anguish or struggling as hypnosis gradually became established.

Fowler (1940) recommended the administration of chloral hydrate as a 7 per cent or a 12.5 per cent solution. His suggested rate of administration

was 1 pint over a 15-minute period. The administration is continued until the corneal reflex is almost obliterated. The depth of anesthesia will increase for about 2 to 3 minutes following the discontinuance of the injection and will maintain this level for approximately 30 minutes.

Chloral hydrate may also be given by stomach tube. Bemis et. al., (1924) gave 1-1/2 to 2 ounces via a stomach tube and then used a local anesthetic at the surgical site. Fowler (1940) used a combination of intravenous and oral chloral hydrate. For an average 1500 pound horse, he would give 2 ounces by stomach tube followed by 90 grams of chloral hydrate intravenously. Fowler recommended withholding feed and water for 5 hours following chloral hydrate anesthesia.

Danks (1943) recommended the use of a mixture of 12 per cent chloral hydrate and 6 per cent magnesium sulfate in the horse. He found that this mixture was less irritating than chloral hydrate when given perivascularly or intramuscularly by accident. Goffinet (1939) stated that the irritant action of chloral hydrate on the subcutaneous and perivascular tissue when the needle is accidently misplaced had been exaggerated.

Millenbruck and Wallinga (1946) considered chloral hydrate to be undesirable because of excessive floundering during the excitement stage and again during the period of recovery. They further stated that there is considerable danger from the toxicity of chloral hydrate in doses necessary for complete anesthesia, so it must be used with caution. The combination of 2 parts chloral hydrate and 1 part magnesium sulfate produced less excitement with the recovery time remaining approximately the same.

According to Millenbruck (1948), nystagmus and corneal reflexes are predominant guides for determining the dosage of chloral hydrate. When the

oscillatory movement of the eyeball almost stops and the animal takes a deep breath, the stage of surgical anesthesia has been reached.

Fowler (1940) stated that the advantages of chloral hydrate are that the surgeon does not require a skilled anesthetist and there is no irritation of the respiratory system. The disadvantages of chloral hydrate are that it is difficult to regulate the depth of anesthesia, the long period of recovery, and like other anesthetic agents, once it is administered it cannot be withdrawn.

Goffinet (1939) stated that surgical anesthesia is characterized by lateral oscillations of the eyes and slowing down of respirations. The awakening is announced by movement of the legs and head with the duration of recovery varing from 1 to 2 hours.

Fowler (1940) proposed the following criteria for determining the depth of anesthesia in the horse: in the human and some species of the lower animals the corneal reflex is obliterated in the first plane of the third stage, whereas in the horse this reflex does not completely disappear until the beginning of the third plane when anesthesia becomes profound. In the horse nystagmus ceases and the corneal reflex may be obliterated in the second plane of the third stage just before the third plane is reached. Respirations are slow and regular and the pulse is strong and regular. In the third plane of the third stage the corneal reflex is lost. Respirations are regular and completely abdominal and the pulse weakens. Muscular relaxation is complete. The tone of the anal and bladder sphinters relax as the fourth plane is reached. In the fourth plane the pulse rate increases but the force decreases. The pupil frequently dilate, but the dilation of the pupil is lessened to the extent that it may escape notice when chloral hydrate is used as the anesthetic.

Danks (1943) suggested that the second plane of the third stage was corresponding to surgical anesthesia. In the second plane or surgical anesthesia the palpebral reflex is lost and the corneal reflex is weakened or absent. Other characteristics are the absence of nystagmus, strong regular pulse, slow regular abdominal breathing and complete relaxation of the skeletal muscles. Besides surgical anesthesia, Danks also used hypnosis and incomplete surgical anesthesia as distinct categories.

Ford (1951) considered the animal to be in narcosis when the animal made the slightest movement in response to a pinprick. The narcosis described by Ford would correspond to the second plane of the third stage as described by Fowler.

Tavernor (1961) stated that surgical anesthesia was characterized by closure of the eyelids, slow shallow respirations, loss of anal reflex, constriction of the pupil, and the loss of the palpebral reflex. He suggested that the corneal reflex would persist to the point of bulbar paralysis.

SODIUM PENTOBARBITAL

If urea reacts with malonic acid, barbituric acid is formed. By the alteration in the chemical configuration of barbituric acid the various derivatives are created. The barbiturates occur as white crystaline powders and have a bitter taste. The free acids are slightly soluble in alcohol. The sodium salts are soluble in water but decompose upon standing (Groves, 1951).

Barbital is classed as a hypnotic and sedative (Goodman and Gillman, 1941). The derivatives of barbital are classified in the order of the duration of their effect as either long, intermediate, short, or ultrashort.

It is generally accepted that the barbiturates, with the exception of phenobarbital and barbital, are metabolized in the liver. Phenobarbital or barbital are not metabolized in the body and are eliminated by the kidneys.

The principle effect of the barbiturates is the depression of the central nervous system by interfering with the passages of impulses to the cerebral cortex (Sollman, 1948).

Pentobarbital was first used as a general anesthetic in veterinary surgery by Kreutzer, Haigler, and Sweebe in 1931 (Wright, 1952). At the onset the drug was administered by intraperitoneal injection in the dog and cat. Wright (1952) employed pentobarbital sodium as an anesthetic agent in the horse by rapid injection using a pumping apparatus. He also used gravity flow following casting. Wright stated that the rapid injection of 1 grain per 7 pounds provoked deep narcosis and the animal was able to regain his feet in 1 to 2 hours. In the gravity flow method the animal was cast and restrained, and pentobarbital sodium was injected over a 6-minute period to produce anesthesia. Anesthesia was assessed by the degree of muscular relaxation and the loss of response to pricking of the skin. The dose required to induce medium depth anesthesia varied from 1 grain per 5 pounds to 1 grain per 6 pounds. At this depth muscular relaxation was complete, the eyelids drooped, and there was a sluggish corneal reflex present. The pulse was accelerated (80 to 90) and respirations slow (2 to 3 per minute) and deep. Anesthesia was maintained for 30 to 45 minutes. The recovery rate was slow and a period of about 4 hours elapsed before the animal was able to regain its feet. In several cases the period of recovery was associated with marked narcotic excitement and struggling making it necessary to maintain effective restraint.

Sweebe (1936, as reported by Wright in 1952) stated that a dose of 25 to 35 grains of pentobarbital injected intravenously will put a horse "out" on

its feet, but Wright (1952) stated that the animal becomes only hyperesthetic in his experience.

Jones (1961) stated that intravenous barbiturates should not be used in the horse without preanesthetic sedation. Jones et. al., (1960) stated that when using intravenous barbiturates, the speed of induction and duration of the anesthesia depend on the rate of injection of the anesthetic. The dose required for induction of anesthesia by rapid intravenous injection is much smaller than that normally used.

When the injection is made slowly, the barbiturate is taken up by the tissue, (particularly the fatty tissues), so that the concentration reaching the brain is diminished. However, rapid injection leaves little time for migration of the barbiturates into the tissues, and consequently the concentration reaching the brain is relatively higher (Jones et. al., 1960).

If no additional anesthetic is administered following rapid induction, the concentration in the brain falls rapidly due to distribution of the anesthetic from the brain to other tissues. Following slow induction, redistribution of the anesthetic from the brain to other parts of the body occurs more slowly, and the duration of the anesthesia is therefore more prolonged (Jones et. al., 1960).

Arthur et. al. (1953) used 1 grain of pentobarbital sodium per 100 pounds of body weight to reach a state of sedation. Schlotthauer also suggested the dose of pentobarbital sodium required to produce sedation in the horse to be 1 grain per 100 pounds of body weight (as reported by Wright).

Millenbruck and Wallinga (1946) used 175 to 225 grains of pentobarbital sodium for anesthesia but stated that its disadvantages were a prohibitive cost, excitement stage during recovery, and slow recovery.

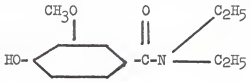
Danks (1943) recommended a dosage of 1 grain of pentobarbital sodium per 15 pounds of body weight for complete anesthesia, 1 grain per 20 pounds of body weight for incomplete anesthesia, and 1 grain per 25 pounds of body weight for hypnosis. Danks also stated that following administration of pentobarbital sodium the patient sometimes fell over backwards and that this movement was dangerous both to the patient and to attendants.

Fowler (1940) found pentobarbital sodium useful in the foal. He recommended a dose of 75 to 375 grains for foals and as high as 1125 grains for older colts. Fowler cited the advantages of pentobarbital sodium anesthesia to be smooth induction, small quantity of solution needed, and little postanesthetic depression. The disadvantages according to Fowler were the prolonged recovery time, expense, and the hazards of its use in the presence of respiratory disorders.

Frank (1959) reported excellent results from the use of pentobarbital sodium as a sedative. He suggested an intravenous dose of 15 grains for a 1,000 pound horse and increasing it for a larger or nervous horse. Frank also stated that pentobarbital sodium is not usually used as a general anesthetic due to its long recovery period and expense involved.

VANILLIC ACID DIETHYLAMIDE

Vanillic acid diethylamide is a white, crystalline powder, that is slightly soluble in water. It was synthesized by Kratzl and Kvasnicka in 1952 (Anderton et. al., 1962). It has the following chemical structure:



The $L.D._{50}$ is 15 mg./kg. intravenously and 90 mg./kg. orally in mice (Romagnoli and Diamond, 1961). They also reported that the respiratory volume increased 100 per cent in rabbits following administration of 2 mg./kg. of VAD intravenously. The response is maximum in 60 seconds and terminates in 10 minutes. Romagnoli and Diamond also reported VAD as 15 times as effective as nikethamide and 4 times as effective as metrazol as a respiratory stimulant. This response occurs irrespective of the depressing cause.

Bernstein (1960) employed VAD as an analeptic agent in 8 cases of barbiturate poisoning in human beings. Ten mg./kg. were given intravenously and repeated at 10-minute intervals until signs of overdosage occurred. The signs of an overdosage as reported by Cole et. al. (1960) are flushing, sneezing, coughing, excitation, diaphoresis, generalized pruritis, and muscular twitching. Cole gave 20 mg./kg. of VAD to patients that had attempted suicide by taking an overdosage of barbiturates. This dose was given over a 6 hour period.

Miller, et. al., (1960) found that VAD stimulated the vasomotor center, exerted an arousal effect, and was a potent respiratory stimulant. When VAD was given intravenously to mice, it caused a marked increase in both frequency and amplitude of respiration and a moderate increase in arterial blood pressure. He injected VAD intravenously in doses of 0.5 to 2 mg./kg. and the effects were noted within 30 seconds and the effects lasted approximately 10 minutes. He found that there was an average increase in tidal respiratory volume of 48 per cent and in respiratory rate of 24 per cent.

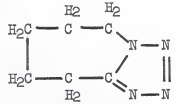
Slater (1962) utilized VAD following anesthesia in man. He found that the most effective time for administering VAD was just after the return of the

swallowing reflex and central fixation of the eyeballs. The average time for the return to a state of orientation and coordination, so the patient might be considered ambulatory, was 15 minutes. All of the patients received a barbiturate 75 minutes preoperatively, either orally or by suppository and adults were given atropine intravenously immediately prior to induction with a thiobarbiturate. Nitrous oxide, halothane, and oxygen combinations were used in either a partial rebreathing or an endotracheal nonrebreathing mask and system. A dosage of 4 mg./kg. of VAD was administered over 1 to 2 minutes starting 4 to 5 minutes following completion of the surgical procedure. Anesthesia had been maintained at plane 1 of stage 3 for most of the surgical operations.

Antelyes (1962) administered doses ranging from 2 to 4 mg./lb. to dogs and cats that had been anesthetized with pentobarbital sodium. Some of the animals were premedicated with a solution of morphine sulfate (1/4 grain/cc.) and atropine sulfate (1/150 grain/cc.) on the basis of 1 cc./25 lb. of body weight. The animals were anesthetized to stage III, plane 3 or 4 for the surgical procedures. Control animals were given anesthetic, with and without premedication. The VAD was given intravenously taking 60 seconds or more. In each of the treated animals there was an immediate increase in depth of respiration. The respiratory rate increase also consistently occurred. Recovery time to partial consciousness or safe level was shortened in all of the VAD trials. The premedicated animals responded more favorably than those that were not premedicated.

PENTYLENETETRAZOL

Pentylenetetrazol was first synthesized in 1923 (Schmidt, 1925) and is classified as a central convulsant drug. It has the structure shown in the accompanying formula.



Pentylenetetrazol directly stimulates and a barbiturate directly depresses the medulla and the cerebral cortex (Pleuger, 1942).

The primary site of action of pentylenetetrazol is in the central nervous system. The principal target cells for pentylenetetrazol are those in the medulla and midbrain. In larger doses its action ascends to the cerebral cortex and descends to the spinal cord (Krantz and Carr, 1961). The action of the drug appears to be one of direct stimulation and not reflexly through the carotid body.

The arousing influence of pentylenetetrazol was extensively studied in narcosis produced by sodium barbital (Tartler, 1937). The same findings were made by Barlow in 1935 using pentylenetrazol on pentobarbital sodium, chloral hydrate, and tribromethanol induced narcosis. In all experiments with barbiturate narcosis in animals, pentylenetetrazol exerted a strong action to arouse the subject in narcosis. Barlow (1946) utilized pentylenetetrazol to awaken dogs from pentobarbital sodium anesthesia by slowly administering the drug until the animal responded and this was generally from 2 to 3 cc. (200 to 300 mg.). Morris and Eastman (1936) also commented on the ability of pentylenetetrazol to shorten injectable barbiturate anesthesia and quoted Fulton and Keller (1932)

as follows: "It (pentylenetetrazol) appears to be a specific stimulant of the cerebral cortex and after anesthetics such as pentobarbital sodium, administration of pentylenetetrazol restores cortical excitability, usually within a period of 5 to 10 minutes after subcutaneous injection."

Alfredson (1941) demonstrated that a therapeutic dose of pentylenetetrazol would increase the average respiratory rate from 3.6 to 19.8 per minutes.

The distribution fate and excretion of pentylenetetrazol has been studied in rats by means of radioactive tagging of pentylenetetrazol. Pentylenetetrazol concentrates in the liver and the major route of excretion is the kidney where most of the excretion occurs within 48 hours (Esplin et. al., 1954).

MATERIALS AND METHODS

Eight horses were utilized in the study. Four of the animals were females and 4 were castrated males. Ages of the experimental animals ranged between 18 months and 30 years. The weights ranged between 136 and 477 kilograms. Table 1 shows the age, sex, and weight of each of the experimental animals.

Table 1. Age, sex, and weight of experimental animals

Horse No.	Age (years)	Weight (kilograms)	Sex
1	2	136	male
3	30	277	female
4	6	466	male
5	1-1/2	236	female
6	13	473	female
7	7	436	male
11	1-1/2	200	female
12	7	477	male

Each animal was anesthetized 8 times with either pentobarbital sodium[1] or a mixture of chloral hydrate-magnesium sulfate[2]. Thirty-five trials were conducted with pentobarbital sodium and 29 trials were conducted with chloral hydrate-magnesium sulfate as the anesthetic. Fifteen control trials were conducted with pentobarbital sodium as the anesthetic agent. Eleven control trials were conducted with chloral hydrate-magnesium sulfate as the anesthetic agent. Table 2 illustrates the breakdown of the anesthetic trials.

Table 2. Breakdown of experimental trials.

Horse No.	P	PV	P_p	C	CV	C_p	Total
1	2	2	1	1	1	1	8
3	3	1	1	1	1	1	8
4	2	2	1	1	1	1	8
5	1	1	2	1	1	2	8
6	2	1	1	1	2	1	8
7	2	1	1	2	1	1	8
11	1	0	3	2	1	1	8
12	2	1	1	2	1	1	8
Total	15	9	11	11	9	9	64

P = Pentobarbital sodium
PV = Pentobarbital sodium with VAD
P_p = Pentobarbital sodium with pentylenetetrazol
C = Chloral hydrate-magnesium sulfate
CV = Chloral hydrate-magnesium sulfate with VAD
C_p = Chloral hydrate-magnesium sulfate with pentylenetetrazol

[1]"Diabutal"; Diamond Laboratories; Des Moines, Iowa.
[2]"Relaxan"; Pitman-Moore Company, Indianapolis, Indiana.

Table 3 shows the order in which the trials were run. Each animal served as its own control, this being necessitated by the individual variation in response to the anesthetic agents. Each animal had at least 2 control trials, one while under pentobarbital sodium induced anesthesia and one under chloral hydrate-magnesium sulfate induced anesthesia. At least 4 days were allowed between any 2 of the anesthetic trials and at least 8 days were allowed between any 2 pentobarbital sodium induced anesthetic trials or between any chloral hydrate-magnesium sulfate induced anesthetic trials.

Table 3. Order of experimental trials.

Horse No.	Trial No. 1	Trial No. 2	Trial No. 3	Trial No. 4	Trial No. 5	Trial No. 6	Trial No. 7	Trial No. 8
1	P	C	PV	C_p	P_p	CV	P	PV
3	P	CV	PV	C_p	P_p	C	P	P
4	P	C_p	PV	C	PV	P_p	CV	P
5	P	C_p	P_p	C	C_p	PV	CV	P_p
6	C	P	CV	C_p	P_p	CV	PV	P
7	P	C	P_p	CV	PV	C_p	P	C
11	P_p	C	CV	P	P_p	C_p	C	P_p
12	PV	C	P_p	C_p	P	CV	P	C

P = Pentobarbital sodium
PV = Pentobarbital sodium with VAD
P_p = Pentobarbital sodium with pentylenetetrazol
C = Chloral hydrate-magnesium sulfate
CV = Chloral hydrate-magnesium sulfate with VAD
C_p = Chloral hydrate-magnesium sulfate with pentylenetetrazol

The injections of all the drugs were into the jugular vein via a 16-gauge 1-1/2" needle. All injections of pentobarbital sodium and pentylenetetrazol were made utilizing a hypodermic syringe. Injections of chloral hydrate-

magnesium sulfate and VAD were made either with a hypodermic syringe or by gravity flow via an intravenous tube.

The initial doses of anesthetic agents were sufficient to produce a state of narcosis or surgical anesthesia. In subsequent trials, the initial dose of the anesthetic was given, and if the animal did not become anesthetized the dosage of the anesthetic agent was increased. Horses No. 5, 11, and 12 required an increase in dosage of pentobarbital sodium to produce a state of narcosis following the initial trials. Horse No. 5 received 9.6 mg./kg. of pentobarbital sodium in the initial trial. The same dosage was given in the fourth pentobarbital trial (anesthetic trial No. 7, graph 6) but a state of narcosis was not attained, so the dosage was increased to 13.7 mg./kg. of pentobarbital sodium. Horse No. 11 required an initial dose of 7.5 mg./kg. of pentobarbital sodium to produce narcosis. On the second pentobarbital sodium trial (anesthetic trial No. 4, graph 9) 9.75 mg./kg. was needed to produce a state of narcosis. On the third pentobarbital sodium trial (anesthetic trial No. 5, graph 9), 9.75 mg./kg. was administered which produced a state of sedation. Consequently the dose of pentobarbital sodium was increased to 14.6 mg./kg., and a state of surgical anesthesia attained. In trial No. 4 on horse No. 11 (anesthetic trial No. 8, graph 9) 14.6 mg./kg. of pentobarbital sodium was administered, and a state of sedation was attained. Again the dose was increased. This time a dose of 18 mg./kg. was required to produce a state of narcosis. A total of 69.0 mg./kg. of pentobarbital sodium was administered over a period of 86 minutes in order to maintain anesthesia while a cast was placed on a left foreleg fracture of the third metacarpal. Horse No. 12 received an initial dosage of 12.3 mg./kg. of pentobarbital sodium, but on the fourth pentobarbital sodium trial (anesthetic trial No. 7, graph 10) the 12.3 mg./kg. failed to produce a state of narcosis. The dosage

was increased to 15.6 mg./kg. in order to produce the desired level of anesthesia.

Horses No. 5 and 7 required increases over the initial dosages needed to produce a state of narcosis in the trials with chloral hydrate-magnesium sulfate. Horse No. 5 received a dose of 76 mg./kg. of chloral hydrate for the first 2 chloral hydrate-magnesium sulfate induced anesthetic trials (anesthetic trials 2 and 4, graph 6). On the second chloral hydrate-magnesium sulfate induced anesthetic trial (trial No. 4, graph 6), the animal did not attain a state of narcosis. This was one of the first trials to indicate the development of an increased tolerance to chloral hydrate-magnesium sulfate, and since this was a control trial, the dosage was not increased. In the third chloral hydrate-magnesium sulfate trial (trial No. 5, graph 6), the dosage was increased to 108 mg./kg. of chloral hydrate from the original 76 mg./kg., before a state of surgical anesthesia was attained.

Horse No. 7 required an initial dose of 82 mg./kg. of chloral hydrate for the first chloral hydrate-magnesium sulfate induced anesthesia trial. On the second trial with this drug (trial No. 4, graph 8) it was necessary to increase the dosage of chloral hydrate from 82 mg./kg. to 113 mg./kg., to attain a state of narcosis. When the same dosage of 113 mg./kg. of chloral hydrate-magnesium sulfate was administered in the third trial (trial No. 6, graph 8), a state of narcosis was again achieved. However, in the fourth trial with the same drug (trial No. 8, graph 8), when the same dosage of 113 mg./kg. of chloral hydrate was administered, a state of narcosis was not produced.

The use of VAD or pentylenetetrazol as arousal agents in the equine species has not been reported; consequently, their most effective dosage and rate of

administration have not been determined. In an attempt to arrive at the most effective method for the administration of these drugs, the dosage and rate of administration were varied in the trials. The following table shows the dosage range of the arousal agents.

Table 4. Dosage range of arousal agents.

Arousal Agent	mg./kg.	Anesthetic Agent
VAD	1.0-9.3	Pentobarbital sodium
VAD	3.2-7.7	Chloral hydrate-magnesium sulfate
Pentylenetetrazol	4.2-15.4*	Pentobarbital sodium
Pentylenetetrazol	4.2-12.3	Chloral hydrate-magnesium sulfate

* Horse No. 11 received a total of 30 mg./kg. over a period of 30 minutes.

Another factor which might affect the success of an arousal agent would be the level of anesthesia at the time of administration. Ideally this would be the level at which the administration of an arousal agent would enable the horse to stand in the shortest time possible, with a minimal amount of incoordination, and to bypass the excitement stage of recovery. In an attempt to ascertain the ideal level of anesthesia for use of arousal agents, they were administrated to animals in which the level varied from narcosis to surgical anesthesia.

Throughout the individual trials observations were made as to respirations per minute, pulse rate, standing time[1], arousal time[2], muscular relaxation, pin

[1]Standing time is that time which elapses between the time that the animal falls to the ground in lateral recumbency and the time that it is able to stand under its own control.

[2]Arousal time is that time which elapses between the time that the arousal agent is administered until the animal is able to stand under its own control.

reflexes of the anus and skin over the withers, nystagmus, palpebral reflex, and corneal reflex. Recordings were made at 5-minute intervals and any special comments as to the general condition of the horse were noted.

The state of anesthesia was classified as sedation[1], narcosis[2], or surgical anesthesia[3]. Because of the difficulty in classifying the border line cases, it was believed that attempts to further separate the classifications would only serve to confuse the picture.

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[1]Sedation is that state where the animal is still able to maintain its feet, but is incoordinated and the response to any painful stimuli is reduced.

[2]Narcosis is that state where the animal is unable to maintain its feet, response to painful stimuli is almost absent, nystagmus is present, muscular relaxation is incomplete, and some form of restraint would be necessary in order to perform surgery. This is the state where most of the surgery is accomplished with the exception of orthopedic or major abdominal surgery.

[3]Surgical anesthesia is that state where there is no response to painful stimuli, nystagmus may cease, good muscular relaxation, and surgery can be performed without any form of restraint.

RESULTS

Since recordings of every trial were kept in detail, it was necessary to condense these trials into table forms so that conclusions could be made. Tables 5 through 10 are a condensation of the 64 trials.

Table 5 shows the results of the control trials with pentobarbital sodium as the anesthetic agent. The horse No., trial No., mg./kg. of pentobarbital sodium given, the plane of anesthesia that was attained, and the standing time from onset of anesthesia are also shown.

Table 6 shows the horse No., trial No., mg./kg. of pentobarbital sodium given, mg./kg. of VAD given, plane of anesthesia attained, standing time, and arousal time following the administration of VAD. Table 7 is identical to table 6 with the exception that pentylenetetrazol was used instead of VAD.

Table 8 shows the control trials with a mixture of chloral hydrate-magnesium sulfate as the anesthetic agent. The horse No., trial No., mg./kg. of chloral hydrate given, mg./kg. of magnesium sulfate given, plane of anesthesia that was attained, and the standing time from the onset of the anesthesia.

Table 9 shows the horse No., trial No., mg./kg. of chloral hydrate and magnesium sulfate given, plane of anesthesia attained, standing time, and arousal time following the administration of VAD. Table 10 is identical to table 9 with the exception that pentylenetetrazol was used instead of VAD.

Table 5. Standing time of subjects anesthetized with pentobarbital sodium without subsequent administration of arousal agents.

Horse No.	Trial No.	mg./kg.	Plane of Anesthesia	Standing Time
1	1	14.0	Surgical	60 minutes
1	4	14.0	Surgical	75 minutes
3	1	8.1	Narcosis	38 minutes
3	4	8.1	Narcosis	21 minutes
3	5	8.1	Sedation	0
4	1	12.0	Narcosis	36 minutes
4	5	12.0	Narcosis	13 minutes
5	1	9.6	Narcosis	38 minutes
6	1	9.6	Surgical	72 minutes
6	4	9.6	Narcosis	40 minutes
7	1	14.3	Narcosis	33 minutes
7	4	14.3	Narcosis	22 minutes
11	2	9.75	Narcosis	46 minutes
12	3	12.3	Narcosis	30 minutes
12	4	15.6	Narcosis	23 minutes

Table 6. Standing times of subjects anesthetized with pentobarbital sodium trials with administration of VAD as the arousal agent.

Horse No.	Trial No.	Pentobarbital mg./kg.	VAD mg./kg.	Plane of Anesthesia	Standing Time	Arousal Time
1	2	14.0	6.0	Surgical	51 minutes	40 minutes
1	5	14.0	9.3	Surgical	45 minutes	4 minutes
3	2	8.1	3.6	Narcosis	36 minutes	6 minutes
4	2	12.0	3.2	Narcosis	19 minutes	4 minutes
4	3	12.0	5.4	Narcosis	28 minutes	10 minutes
5	3	9.6	2.1	Narcosis	64 minutes	7 minutes
6	3	9.6	3.2	Surgical	30 minutes	3 minutes
7	3	14.3	3.4	Narcosis	20 minutes	4 minutes
12	1	12.3	1.0	Narcosis	19 minutes	1 minute

Table 7. Standing times of subjects anesthetized with pentobarbital sodium trials with administration of pentylenetetrazol as the arousal agent.

Horse No.	Trial No.	Pentobarbital mg./kg.	Pentylenetetrazol mg./kg.	Plane of Anesthesia	Standing Time	Arousal Time
1	3	14.0	15.4	Surgical	24 minutes	45 seconds
3	3	8.1	7.1	Narcosis	16 minutes	50 seconds
4	4	12.0	4.3	Narcosis	19 minutes	3 minutes
5	2	9.6	8.4	Narcosis	18 minutes	30 seconds
5	4	13.7	19.0*	Surgical	98 minutes	48 seconds
6	2	9.6	13.6**	Surgical	50 minutes	29 minutes
7	2	14.3	4.6	Narcosis	17 minutes	10 minutes
11	1	7.5	12.5	Surgical	47 minutes	27 minutes
11	3	14.6	10.0	Surgical	113 minutes	7 minutes
11	4	69.0***	30.0****	Surgical	190 minutes	30 minutes
12	2	12.3	4.2	Narcosis	15 minutes	40 seconds

* Injections of 2500 mg at 10 minutes and 2000 mg at 98 minutes.

** 3000mg of pentylenetetrazol was administered at 21 minutes and horse was able to raise head. At 25 minutes 1000 mg more was given and 1000 mg more at 45 minutes.

*** 13,800 mg pentobarbital given over 86 minutes. 18 mg./kg. was administered to produce a state of narcosis.

**** 3000 mg pentylenetetrazol given at 160 minutes. Arousal action to the extent that the horse was able to sit. Respirations increased from 7 to 12 per minute.

Table 8. Standing times of subjects anesthetized with chloral hydrate-magnesium sulfate without subsequent administration of arousal agents.

Horse No.	Trial No.	C.H.	$MgSO_4$	Plane of Anesthesia	Standing Time
1	1	110	92	Narcosis	120 minutes
3	3	131	112	Narcosis	210 minutes
4	2	119	99	Narcosis	42 minutes
5	2	76	64	Sedation	0
6	1	79	66	Narcosis	45 minutes
7	1	82	69	Narcosis	75 minutes
7	4	113	95	Sedation	0
11	1	128	107	Narcosis	30 minutes
11	4	128	107	Narcosis	13 minutes
12	1	110	92	Narcosis	37 minutes
12	4	110	92	Narcosis	14 minutes

Table 9. Standing times of subjects anesthetized with chloral hydrate-magnesium sulfate trials with administration of VAD as the arousal agent.

Horse No.	Trial No.	C.H. Mg./Kg.	$MgSO_4$ Mg./Kg.	VAD Mg./Kg.	Plane of Anesthesia	Standing time	Arousal Time
1	3	110	92	7.7*	Surgical	57 minutes	7 minutes
3	1	121	112	5.4**	Narcosis	67 minutes	11 minutes
4	3	119	99	4.3***	Narcosis	35 minutes	5 minutes
5	4	101	85	6.4	Surgical	77 minutes	64 minutes
6	2	79	66	3.2	Narcosis	63 minutes	20 minutes
6	4	79	66	5.3	Narcosis	61 minutes****	60 minutes
7	2	113	95	3.2	Narcosis	50 minutes	2 minutes
11	2	128	107	7.5	Narcosis	21 minutes	1 minute
12	3	110	92	4.2	Narcosis	32 minutes	20 minutes

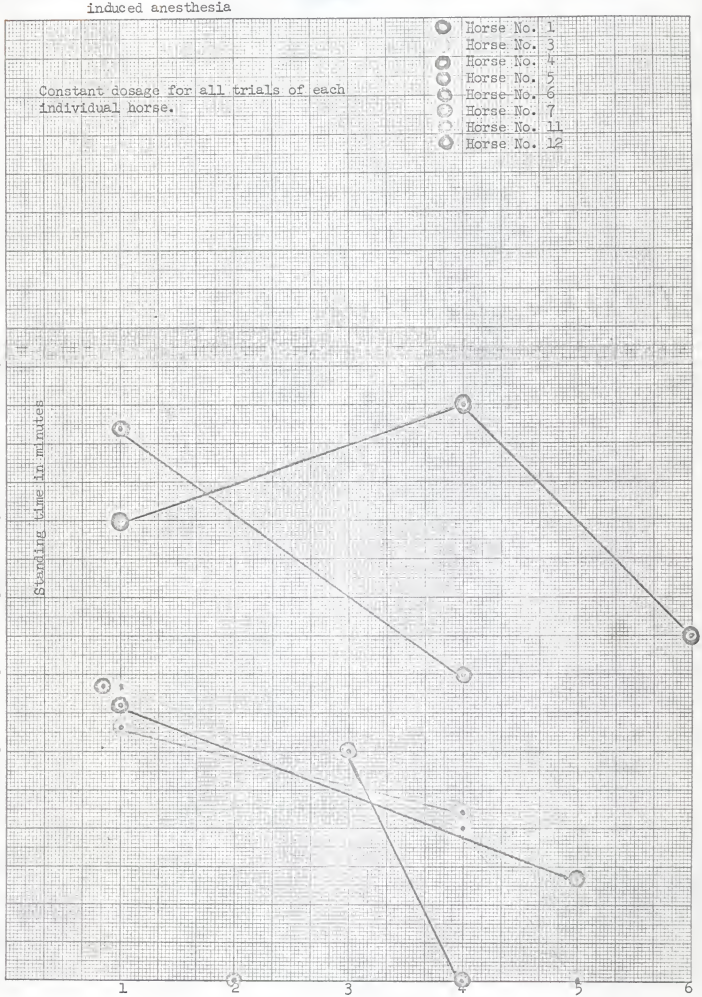
* Injected intravenously in one minute.
** Injected intravenously over four minutes.
*** Diluted in 500 cc physiological saline and given over a four-minute period.
**** Horse fell in sternal recumbency and VAD was started immediately.

Table 10. Standing times of subjects anesthetized with chloral hydrate-magnesium sulfate with administration of pentylenetetrazol as the arousal agent.

Horse No.	Trial No.	C.H. Mg./Kg.	$MgSO_4$ Mg./Kg.	Pentylenetetrazol Mg./Kg.	Plane of Anesthesia	Standing Time	Arousal Time
1	2	110	92	12.3	Surgical	32 minutes	30 seconds
3	2	131	112	9.0	Narcosis	57 minutes	40 seconds
4	1	119	99	4.3	Narcosis	16 minutes	10 minutes*
5	1	76	64	8.5	Narcosis	12 minutes	51 seconds
5	3	108	90	10.6	Surgical	20 minutes	1 minute
6	3	79	66	5.3	Narcosis	26 minutes	45 seconds
7	3	113	95	4.6	Narcosis	10 minutes	50 seconds
11	3	128	107	7.5	Narcosis	11 minutes	45 seconds
12	2	110	92	4.2	Narcosis	36 minutes	2 minutes

* The 4.3 mg./kg. was administered by two equal doses at a ten-minute interval. Time is indicated from the time of the first injection.

Graph 1. Standing times of the control trials with pentobarbital sodium induced anesthesia



GRAPH 1

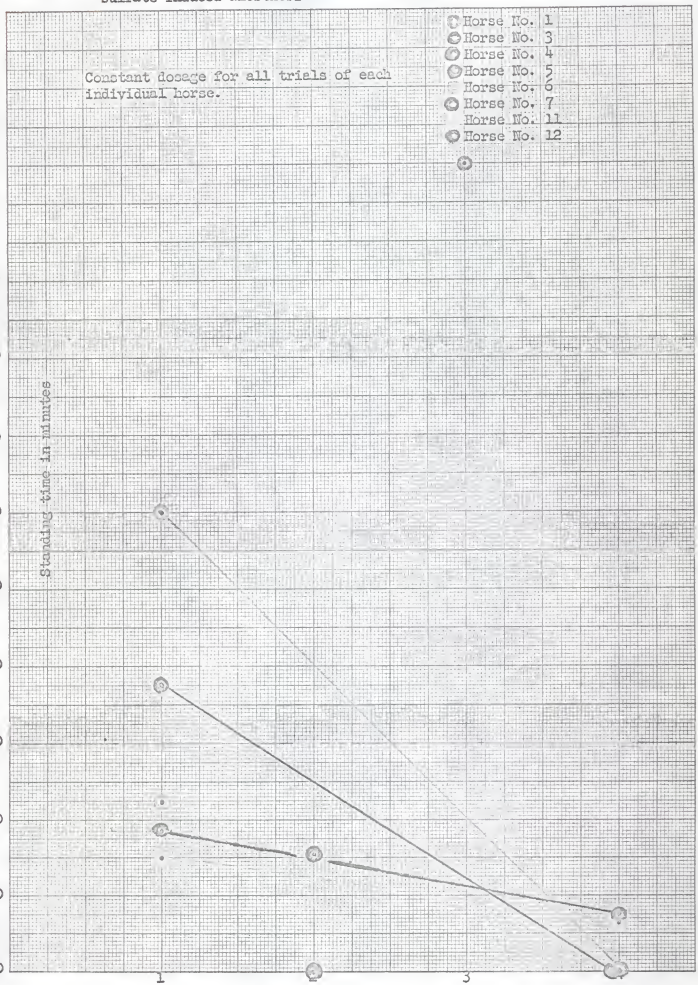
Graph 1 illustrates the standing times of the control trials of all horses anesthetized with pentobarbital sodium. These control trials had a dual purpose. They established normal standing times to be used as criteria by which to judge the effectiveness of the arousal agents, and they were also necessary to determine if the animals were developing increased tolerance to the anesthetic agents. Therefore, control trials were interspersed among the experimental trials as indicated in table 3.

The graph indicates that with the exception of hose No. 1, an increased tolerance was developed in all animals which underwent two or more control trials. Conversely, the second control trial with horse No. 1 showed an increase in standing time rather than a decrease. Therefore, a third control trial was run (trial No. 6 of pentobarbital sodium), and a decrease in standing time did occur. This decrease was 30 minutes under the second control trial and 15 minutes under the initial control trial.

Horses No. 5 and 11 each underwent only one control trial with pentobarbital sodium, and this is indicated on the graph. But the reaction of these horses to pentobarbital sodium in the experimental trials gave evidence that they also were developing an increased tolerance to this drug.

In the fourth experimental pentobarbital sodium induced anesthesia trial with horse No. 5 (anesthetic trial No. 7, table 16), the initial dose of 9.6 mg./kg. failed to anesthetize the animal, so the dosage was increased to 13.7 mg./kg. and a state of narcosis was then attained. Horse No. 11 received an initial dose of 7.5 mg./kg. in the first experimental pentobarbital sodium induced anesthesia trial, but later, in the only control trial with this horse (anesthetic trial No. 4, graph 9), 9.75 mg./kg. was administered before a state of narcosis was attained.

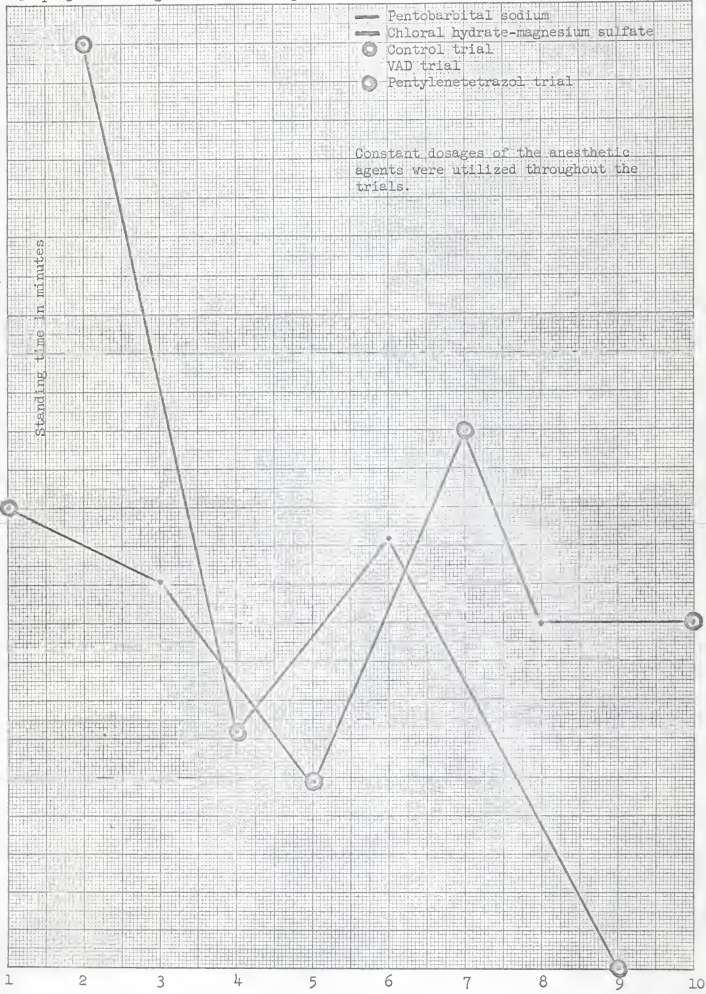
Graph 2. Standing times of the control trials with chloral hydrate-magnesium sulfate induced anesthesia



GRAPH 2

Graph 2 illustrates the chloral hydrate-magnesium sulfate induced anesthesia control trials of all of the horses. The purpose of the trials was to establish normal standing times which could be used as criteria by which to judge the effectiveness of the arousal agents, and to determine if the animals were developing an increased tolerance to chloral hydrate-magnesium sulfate. As indicated on the graph, an increased tolerance was developed to chloral hydrate-magnesium sulfate in horses No. 1, 7, 11, and 12. Horse No. 5 might also be added to this list even though it underwent only one control trial. This trial was the second trial with this drug and the initial dose failed to produce a state of narcosis. She received a dosage of 76 mg./kg. for the first experimental chloral hydrate-magnesium sulfate induced anesthesia trial (anesthetic trial No. 2, graph 6), but in the control trial (anesthetic trial No. 4, graph 6), the 76 mg./kg. failed to produce a state of narcosis. Horses No. 3, 4, and 6 received a constant dosage of the anesthetic agent throughout the experiment. Horses No. 3 and 4 each underwent 3 chloral hydrate-magnesium sulfate induced anesthesia trials and horse No. 6 underwent 4 trials with this anesthetic agent. However with each of these horses only 1 of the trials was a control trial which made it impossible to judge possible increased tolerance on the basis of control trials.

Graph 3. Standing times of the experimental and control trials with horse No. 1



GRAPH 3

Graph 3 shows a comparison in graph form of the standing times of all the anesthetic trials conducted on horse No. 1. The control trials are circled in black, VAD trials in blue, and pentylenetetrazol trials in red. The standing times of the pentobarbital sodium induced anesthesia trials are connected by a black line, and the standing times of the chloral hydrate-magnesium sulfate induced anesthesia trials are connected by a red line. Six trials were conducted with pentobarbital sodium, and 4 trials with chloral hydrate-magnesium sulfate.

A constant dosage of 14.0 mg./kg. was used in all pentobarbital sodium induced anesthesia trials, and a constant dosage of 110 mg./kg. of chloral hydrate (92 mg./kg. of magnesium sulfate) was used throughout the chloral hydrate-magnesium sulfate induced anesthesia trials. In trial 9 the animal did not become anesthetized with the dose of chloral hydrate-magnesium sulfate administered. This was a control trial.

Trial No. 1 was a control trial with pentobarbital sodium. A state of surgical anesthesia was attained and respirations ranging from 10 to 14 per minute were recorded. The first arousal movements occurred at 49 minutes. At 60 minutes the animal was able to stand but was very incoordinated when trying to walk for the next 11 minutes.

Trial No. 2 was a control trial with chloral hydrate-magnesium sulfate. A state of narcosis was attained with respirations ranging from 14 to 20 per minute. Twenty-two minutes following induction some slight arousal movements occurred. At 45 minutes the animal was able to lift its head, and at 63 minutes it made a feeble attempt to stand. Several more feeble attempts occurred before it was able to stand at 120 minutes.

Trial No. 3 was an experimental trial utilizing 6.0 mg./kg. of VAD following pentobarbital sodium induced anesthesia. The drug was given over an 18 minute period starting 11 minutes postinduction. A chewing reflex with voluntary head movement occurred at 33 minutes, and at 39 minutes the animal was able to raise its head. Standing occurred at 51 minutes, and the animal could walk with only slight incoordination. Respirations ranged from 9 to 12 per minute throughout the trial.

Trial No. 4 was an experimental trial utilizing 12.3 mg./kg. of pentylenetetrazol following chloral hydrate-magnesium sulfate induced anesthesia. Pentylenetetrazol was administered over a 30 second period starting 31 minutes after induction of the anesthesia. Thirty seconds after completion of administration of the drug the animal was standing. Respirations ranged from 10 to 14 per minute during the trial. No recording of respiration was made after the injection of the drug because of the arousal movements and the standing of the animal.

Trial No. 5 was an experimental trial utilizing 15.4 mg./kg. of pentylenetetrazol following pentobarbital sodium anesthesia. Pentylenetetrazol was administered over a 1 minute period starting 23 minutes after induction of the anesthesia. Standing occurred 45 seconds after completion of the administration. Respirations ranged from 12 to 13 per minute prior to the injection of the drug. No postinjection recordings were made on respirations per minute.

Trial No. 6 was an experimental trial with VAD following chloral-hydrate-magnesium sulfate induced anesthesia. Fifty minutes after induction of anesthesia, vanillic acid diethylamide was administered over a 1 minute period at a dosage of 7.7 mg./kg. Apnea occurred for a 30 second period

following the injection, followed by a period of clonic and tonic spasms for a period of 4 minutes. Respirations ranged from 14 to 18 per minute prior to administration of the drug. The respirations increased to 48 per minute at 4 minutes postinjection of VAD. The animal was able to stand in 7 minutes following administration of the VAD.

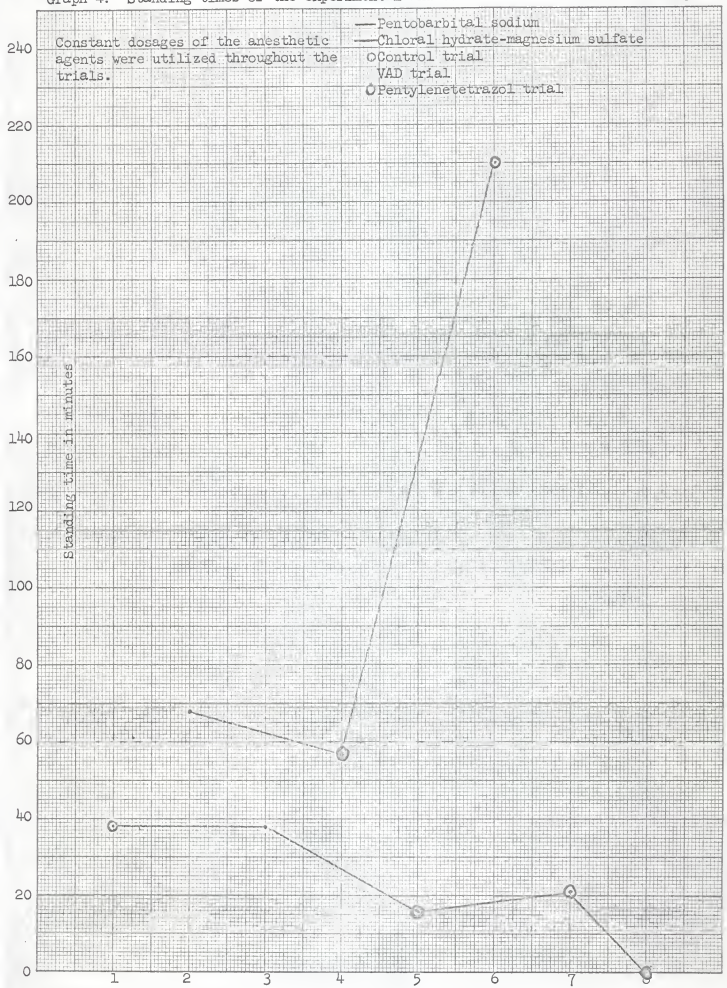
Trial No. 7 was the second control trial with pentobarbital sodium induced anesthesia, and a state of surgical anesthesia was again attained. Respirations ranged from 9 to 20 per minute. The 20 per minute occurred as the animal was starting to arouse from the anesthesia. At 70 minutes the animal was able to hold its head up, and it was walking at 75 minutes.

Trial No. 8 was the second VAD experimental trial following pentobarbital sodium induced anesthesia. A state of surgical anesthesia was attained. Respirations ranged from 9 to 14 per minute. A dose of 9.3 mg./kg. of VAD was administered 42 minutes after induction of the anesthesia. This amount was administered over a 2 minute period and arousal actions occurred. A very few clonic spasms occurred, and the animal was standing in 4 minutes. The respirations increased from 13 to 25 per minute following injection of VAD. Six minutes later the respirations were back to the 13 per minute.

Trial No. 9 was a second control trial run with chloral hydrate-magnesium sulfate induced anesthesia. The same dosage used in the first 3 trials with this drug failed to produce a state of narcosis.

Trial No. 10 was the third control trial with pentobarbital sodium anesthesia conducted on this horse. Trial No. 9 is included in graph 1, and No. 10 is included in graph 2, but they are not listed in the materials and methods of this experiment because they were supplemental to the original plan of 8 trials per animal.

Graph 4. Standing times of the experimental and control trials with horse No. 3.



GRAPH 4

Graph 4 shows a comparison of the standing times of all anesthetic trials conducted on horse No. 3. The graph is constructed in the same manner as graph 3. Five trials were conducted with pentobarbital sodium anesthesia and 3 were conducted with chloral hydrate-magnesium sulfate anesthesia.

A constant dosage of the anesthetic agents was used throughout their respective trials. In trial No. 8 the animal did not become anesthetized with the initial dose, but this was a control trial and it was not considered necessary to induce narcosis.

Trial No. 1 was a control trial utilizing pentobarbital sodium as the anesthetic. A state of narcosis was attained and the respirations ranged from 18 to 20 per minute. Arousal movements occurred at 30 minutes postinduction, and standing occurred at 38 minutes.

Trial No. 2 was an experimental trial utilizing VAD following induction of chloral hydrate-magnesium sulfate anesthesia. Respirations ranged from 10 to 13 per minute before the injection of VAD. Arousal movements first occurred at 45 minutes when the animal was able to raise its head. At 56 minutes postinduction, 5.4 mg./kg. of VAD was administered over a 4 minute period. Respirations increased to 20 per minute and the horse was able to stand. The increase in respirations lasted for 5 minutes.

Trial No. 3 was an experimental trial utilizing VAD following induction of pentobarbital sodium anesthesia. Respirations ranged from 8 to 12 per minute before the administration of VAD. At 30 minutes postinduction 3.6 mg./kg. of VAD was administered over a 2 minute period. Respirations increased to 20 per minute, and the increase lasted for 5 minutes. The animal was able to stand at 36 minutes postinduction.

Trial No. 4 was an experimental trial utilizing pentylenetetrazol following induction of chloral hydrate-magnesium sulfate anesthesia. Respirations ranged from 9 to 12 per minute. The animal was able to raise its head 52 minutes following induction of anesthesia. At 57 minutes pentylenetetrazol was administered, and standing occurred in 40 seconds.

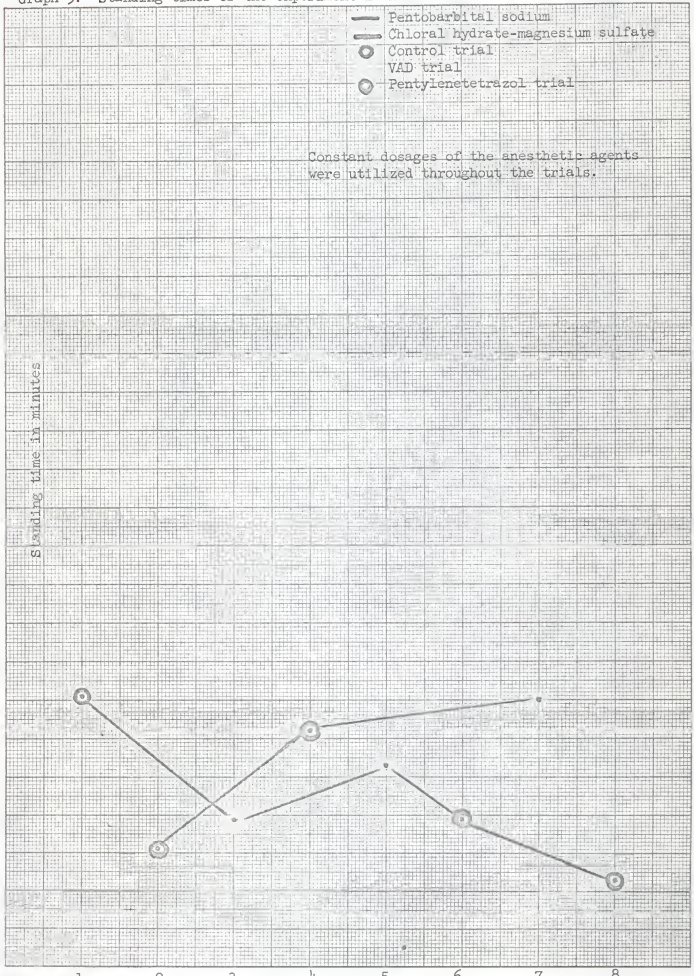
Trial No. 5 was an experimental trial utilizing pentylenetetrazol following pentobarbital sodium induced anesthesia. Respirations ranged from 8 to 10 per minute. At 16 minutes postinduction 7.1 mg./kg. of pentylenetetrazol administered over a 1 minute period resulted in a 30 second standing time.

Trial No. 6 was a control trial with chloral hydrate-magnesium sulfate anesthesia. Respirations ranged from 9 to 12 per minute following induction. At 105 minutes postinduction the animal was able to sit in sternal recumbency, but was unable to stand. Standing finally occurred at 210 minutes postinduction.

Trial No. 7 was a control trial with pentobarbital sodium anesthesia. Respirations ranged from 12 to 18 per minute following induction. An attempt to stand was made at 15 minutes and standing occurred at 21 minutes postinduction.

Trial No. 8 was the third pentobarbital sodium induced anesthesia control trial. The animal did not become anesthetized with the initial dose, and since this was a control trial the dosage was not increased.

Graph 5. Standing times of the experimental and control trials with horse No. 4



GRAPH 5

Graph 5 shows a comparison of the standing times of all the anesthetic trials run on horse No. 4. The graph is constructed in the same manner as graph 3.

Five trials were conducted with pentobarbital sodium and 3 trials with chloral hydrate-magnesium sulfate. A constant dosage of the anesthetic agents was used throughout their respective trials. A state of narcosis was attained in all trials.

Trial No. 1 was a control trial with pentobarbital sodium. Respirations ranged from 12 to 20 per minute. At 21 minutes postinduction the patient made an attempt but was unable to stand. The patient was able to stand with incoordination at 36 minutes postinduction.

Trial No. 2 was an experimental trial utilizing pentylenetetrazol following induction of chloral hydrate-magnesium sulfate anesthesia. The respiratory rate ranged from 16 to 20 per minute. At 5 minutes post-induction 2.15 mg./kg. of pentylenetetrazol was administered, and the animal attained a position of sternal recumbency. No attempt to stand was made so an additional 2.15 mg./kg. was administered with the result that the patient was standing in less than 1 minute following the last injection.

Trial No. 3 was an experimental trial utilizing VAD following pentobarbital sodium induced anesthesia. The respiratory rate ranged from 14 to 16 per minute. A total of 3.2 mg./kg. was administered at 16 minutes postinduction. Tonic spasms occurred followed by about 25 seconds of clonic spasms before the animal was able to stand at 19 minutes postinduction.

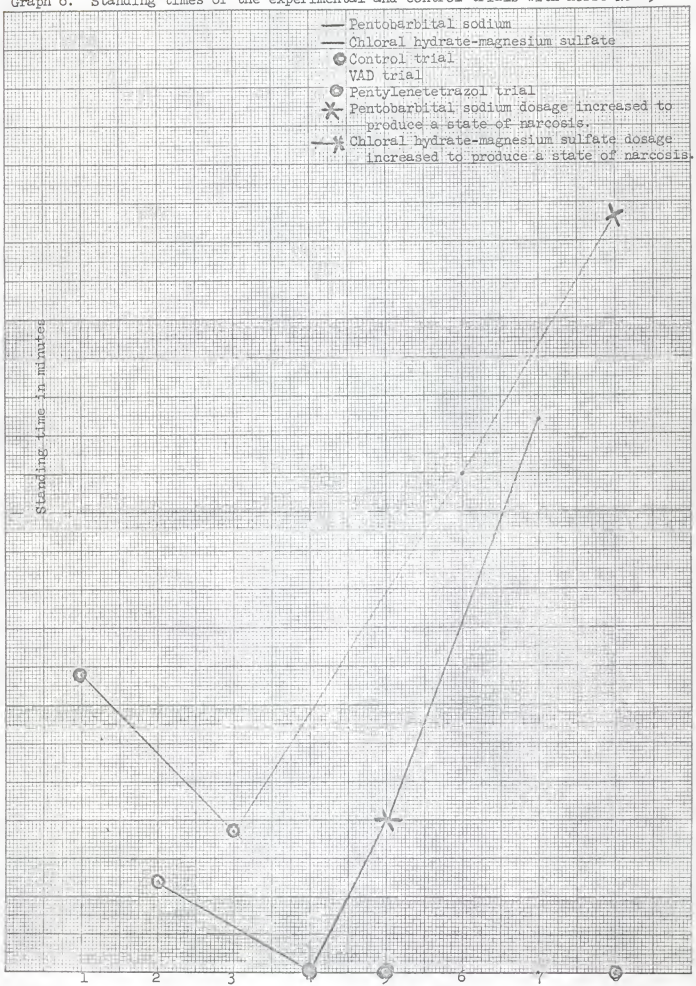
Trial No. 4 was a control with chloral hydrate-magnesium sulfate anesthesia. Respirations ranged from 18 to 20 per minute. At 25 minutes postinduction the patient was able to attain a position of sternal recumbency. At 35 minutes postinduction an attempt to stand was made by the patient, but it was 42 minutes postinduction before standing occurred.

Trial No. 5 was a trial utilizing VAD following pentobarbital sodium anesthesia. Respirations ranged from 10 to 15 per minute. Starting at 18 minutes postinduction, 5.4 mg./kg. of VAD was administered over a 6 minute period. Some tonic and clonic spasms occurred lasting for 2 minutes. The animal was able to stand at 28 minutes postinduction.

Trial No. 6 utilized pentylenetetrazol following pentobarbital sodium anesthesia. Postinduction respirations ranged from 16 to 20 per minute. At 14 minutes the patient was able to raise its head. At 15 minutes, 4.3 mg./kg. of pentylenetetrazol was administered, and the animal was standing within 3 minutes.

Trial No. 7 utilized VAD following chloral hydrate-magnesium sulfate anesthesia. Respirations ranged from 18 to 20 per minute. At 30 minutes postinduction 4.3 mg./kg. of VAD was administered over a 5 minute period. This drug was diluted in 500 ml. of physiological saline and administered by an intravenous set and a 16-gauge needle. The solution was held 40 inches above the jugular vein while the animal was in lateral recumbency. Upon completion of the administration an increase in respirations from 20 to 24 per minute was noted. A period of tonic and clonic spasms occurred following injection and lasted for 1 minute. At 35 minutes postinduction the animal was standing.

Graph 6. Standing times of the experimental and control trials with horse No. 5



GRAPH 6

Graph 6 illustrates a comparison of the standing times of all the anesthetic trials conducted on horse No. 5. Four trials were conducted with pentobarbital sodium and 4 with chloral hydrate-magnesium sulfate.

It was necessary to increase the dosage of both anesthetic agents during the experiment. In the first 3 pentobarbital sodium trials, 9.6 mg./kg. of pentobarbital sodium was given, and a state of narcosis was attained in each trial. In the fourth trial with pentobarbital sodium, 9.6 mg./kg. was administered, but only a state of sedation was attained. The dosage was increased to 13.7 mg./kg. resulting in a state of surgical anesthesia.

In the chloral hydrate-magnesium sulfate trials, 76 mg./kg. of chloral hydrate (64 mg./kg. of magnesium sulfate) was administered in the first trial. In the second trial with chloral hydrate-magnesium sulfate, the dosage utilized in the first trial produced only a state of sedation. Since this was a control trial, no further anesthetic was given. In the third trial with chloral hydrate-magnesium sulfate, it was necessary to increase the dose from 76 mg./kg. to 108 mg./kg. of chloral hydrate (90 mg./kg. of magnesium sulfate) before the animal became anesthetized. Then a state of surgical anesthesia was attained.

Trial No. 1 was a control trial with pentobarbital sodium. Respirations ranged from 11 to 20 per minute. At postinduction time, 27 minutes, the animal was able to raise its head, but it was unable to stand until 38 minutes postinduction.

Trial No. 2 utilized pentylenetetrazol following chloral hydrate-magnesium sulfate anesthesia. Respirations ranged from 12 to 15 per minute with an increase to 30 respirations per minute following the administration of 8.5 mg./kg.

of pentylenetetrazol. This was given at 11 minutes postinduction, and in 51 seconds the animal was able to stand and walk.

Trial No. 3 utilized pentylenetetrazol following pentobarbital sodium induced anesthesia. Respirations ranged from 19 to 22 per minute. The arousal agent was administered at 17 minutes postinduction, and the animal was standing in 30 seconds.

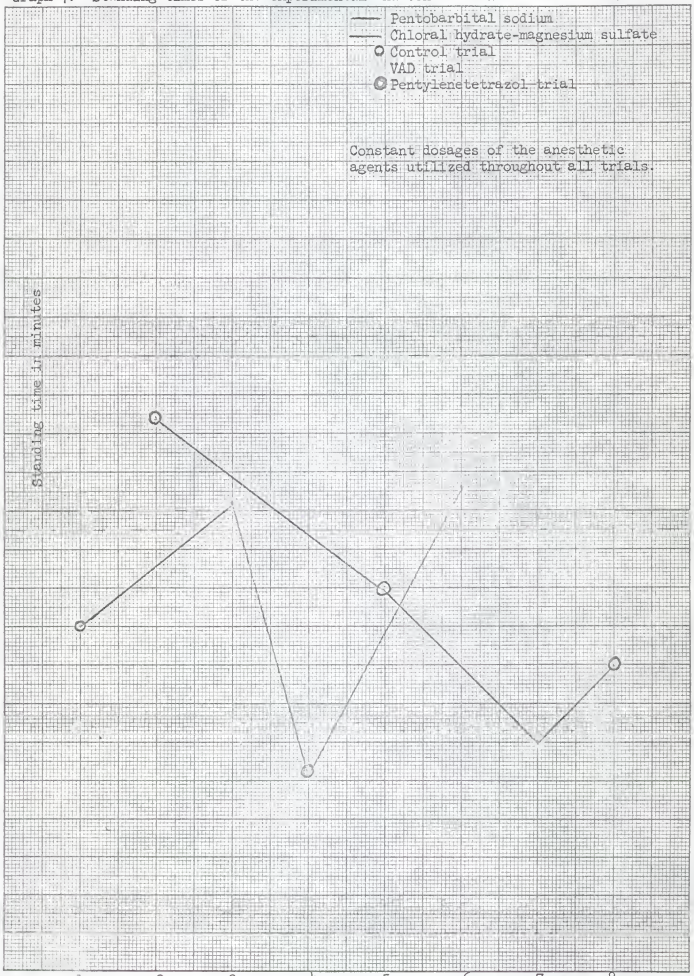
Trial No. 4 was a control trial with chloral hydrate-magnesium sulfate. The 76 mg./kg. of chloral hydrate (64 mg./kg. of magnesium sulfate) produced only sedation with slight incoordination.

Trial No. 5 utilized pentylenetetrazol following chloral hydrate-magnesium sulfate induced anesthesia. The animal did not become anesthetized so the dosage was increased to 108 mg./kg. of chloral hydrate (90 mg./kg. of magnesium sulfate), which resulted in a state of surgical anesthesia of approximately 9 minutes duration. At 20 minutes postinduction a state of narcosis was present and 10.6 mg./kg. of pentylenetetrazol was administered over a 60 second period. The animal was standing and walking 1 minute following the completion of the administration. There was a 10-minute period of incoordination following standing.

Trial No. 6 utilized VAD following pentobarbital sodium induced anesthesia. Respirations ranged from 10 to 12 per minute. At 57 minutes postinduction, 2.1 mg./kg. of VAD was administered over a 3-minute period. Tonic and clonic spasms occurred for about 30 seconds starting 1 minute after completion of the drug administration. Respirations then increased to 22 per minute, and at 64 minutes postinduction the animal was standing.

Trial No. 7 utilized VAD following chloral hydrate-magnesium sulfate induced anesthesia. Respirations ranged from 14 to 15 per minute. The

Graph 7. Standing times of the experimental and control trials with horse No. 6.



dosage of chloral hydrate-magnesium sulfate was increased from 76 mg./kg. of chloral hydrate to 101 mg./kg., (85 mg./kg. of magnesium sulfate) in order to attain a state of surgical anesthesia. At 13 minutes postinduction 6.4 mg./kg. of VAD was administered over a 15-minute period. Tonic and clonic spasms occurred for a 60 second period. At 28 minutes postinduction the patient was able to maintain a position of sternal recumbency. At 77 minutes postinduction the patient was able to stand.

Trial No. 8 utilized pentylenetetrazol following pentobarbital sodium induced anesthesia. Respirations ranged from 1 to 2 per minute before administration of the pentylenetetrazol. It was necessary to increase the dosage of pentobarbital sodium from 9.6 mg./kg. to 13.7 mg./kg., to attain a state of surgical anesthesia. A total of 19.0 mg./kg. of pentylenetetrazol was administered in 2 doses. At 10 minutes postinduction, 10.0 mg./kg. was administered, and the respirations increased from 1 to 17 per minute. This increase in respirations lasted for 10 minutes, at which time the level decreased to 2 per minute. The animal was able to raise its head following administration of the 10.0 mg./kg. of pentylenetetrazol. At 97 minutes postinduction an additional 9.0 mg./kg. of pentylenetetrazol was administered and the animal stood within 48 seconds.

GRAPH 7

Graph 7 shows a comparison of the standing times of all of the anesthetic trials conducted on horse No. 6. The graph is constructed in the same manner as graph 3.

Four of the trials involved pentobarbital sodium and 4 involved chloral hydrate-magnesium sulfate. A constant dosage of the anesthetic agent was used throughout the trials and a state of narcosis was attained in all trials.

Trial No. 1 was a control trial with chloral hydrate-magnesium sulfate anesthesia. Respirations ranged from 12 to 15 per minute. At 37 minutes post-induction, the animal made an attempt to attain sternal recumbency and at 45 minutes postinduction he was able to stand and walk although incoordinated.

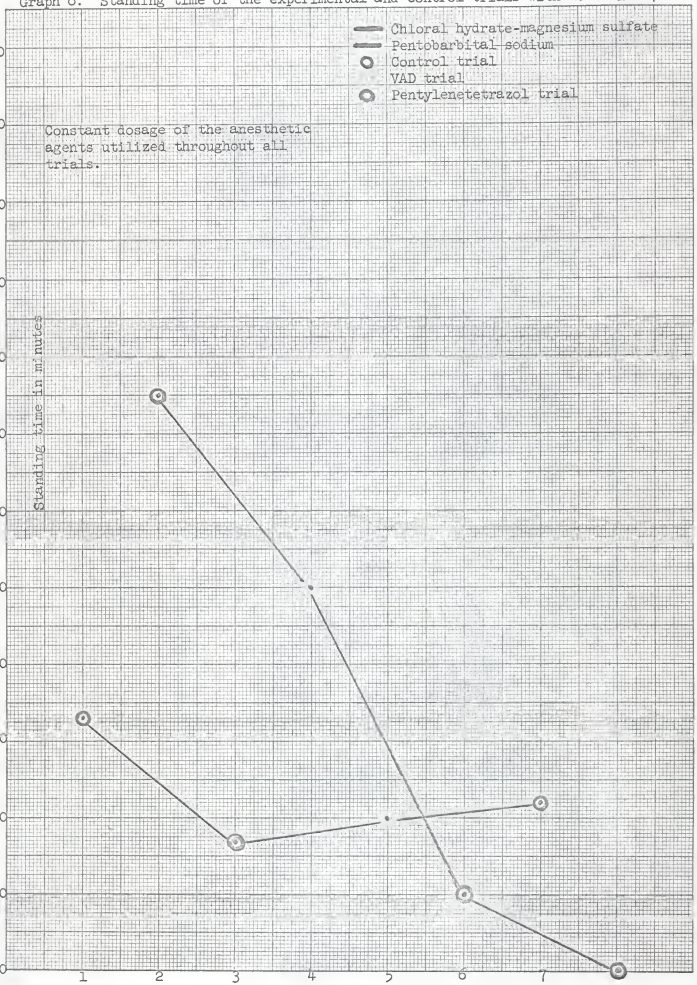
Trial No. 2 was a control trial involving pentobarbital sodium. The respiratory rate ranged from 12 to 18 per minute. At 45 minutes postinduction there was some movement of the head, and at 65 minutes the animal attained a position of sternal recumbency. Standing occurred at 72 minutes, but the animal was very incoordinated.

Trial No. 3 was an experimental trial utilizing VAD following chloral hydrate-magnesium sulfate anesthesia. Respirations ranged from 12 to 14 per minute. At 43 minutes postinduction, 3.2 mg./kg. of VAD was given and the patient responded by lifting its head. Respirations increased from 14 to 18 per minute. No tonic or clonic spasms were observed. Standing occurred at 63 minutes postinduction.

Trial No. 4 was an experimental trial utilizing pentylenetetrazol following chloral hydrate-magnesium sulfate induced anesthesia. Respirations ranged from 10 to 32 per minute. At 21 minutes postinduction the horse was able to attain a position of sternal recumbency. At 25 minutes postinduction 5.3 mg./kg. of pentylenetetrazol was given, and resulted in the patient standing within 45 seconds.

Trial No. 5 was an experimental trial utilizing pentylenetetrazol following pentobarbital sodium anesthesia. Respirations ranged from 14 to 24 per minute. Starting at 21 minutes postinduction, 13.6 mg./kg. of pentylenetetrazol was administered over a 24 minute period. The horse was able to stand at 50 minutes postinduction.

Graph 8. Standing time of the experimental and control trials with horse No. 7



Trial No. 6 utilized VAD following chloral hydrate-magnesium sulfate induced anesthesia. Following administration of the anesthetic agent, 7 minutes elapsed before narcosis was attained. Respirations ranged from 14 to 15 per minute. The arousal agent was diluted in 450 ml. of physiological saline, and a total of 5.3 mg./kg. VAD was administered. This dosage was given over a 3 minute period starting at 7 minutes postinduction. Respirations increased from 14 to 18 per minute. Tonic spasms were noted for a period of 1 minute. At 61 minutes postinduction the animal was able to stand and walk.

Trial No. 7 was an experimental trial utilizing VAD following pentobarbital sodium anesthesia. Respirations ranged from 16 to 18 per minute. At 24 minutes postinduction, 3.2 mg./kg. of VAD was administered over a 3 minute period. The patient was standing at 30 minutes postinduction.

Trial No. 8 was a control trial involving pentobarbital sodium anesthesia. Respirations ranged from 12 to 14 per minute. At 25 minutes postinduction the horse was able to lift its head. At 40 minutes postinduction, standing occurred.

GRAPH 8

Graph 8 shows a comparison of the standing times of the experimental trials conducted on horse No. 7. Four trials were conducted utilizing pentobarbital sodium and 4 utilizing chloral hydrate-magnesium sulfate.

A constant dosage was given throughout the pentobarbital sodium trials and a state of narcosis was attained in each instance.

In the first chloral hydrate-magnesium sulfate trial, 82 mg./kg. of chloral hydrate (69 mg./kg. of magnesium sulfate) was administered, and a state of narcosis was attained. In the second and third trials it was necessary to increase the dosage to produce a state of narcosis. The dosage was increased to

113 mg./kg. of chloral hydrate (95 mg./kg. of magnesium sulfate) in the last 3 trials. In the fourth trial the animal did not attain a state of narcosis; however, additional anesthetic was not given since this was a control trial.

Trial No. 1 was a control trial involving pentobarbital sodium anesthesia. Respirations ranged from 14 to 16 per minute. At 25 minutes postinduction the animal was able to raise its head. At 38 minutes postinduction the animal was able to stand although very incoordinate.

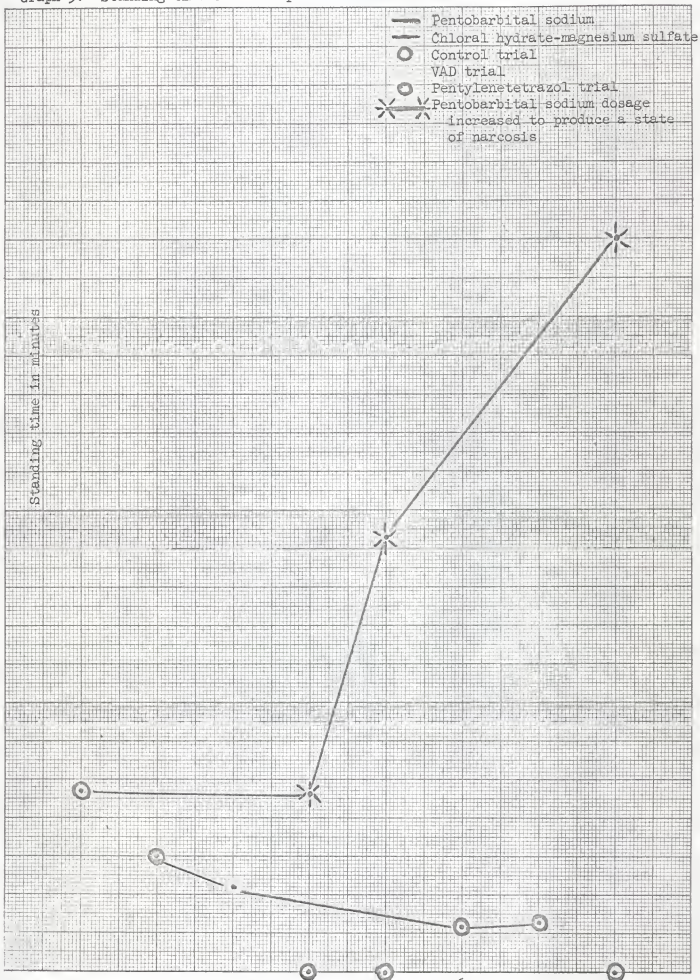
Trial No. 2 was a control trial involving chloral hydrate-magnesium sulfate anesthesia. Respirations ranged from 14 to 15 per minute. At 45 minutes postinduction the animal made an attempt to attain a position of sternal recumbency but was unable to do so. At 65 minutes postinduction an effort was made to stand and at 75 minutes postinduction the patient was able to stand.

Trial No. 3 was an experimental trial utilizing pentylenetetrazol following pentobarbital sodium induced anesthesia. Respirations ranged from 16 to 17 per minute. At 7 minutes postinduction, 4.6 mg./kg. of pentylenetetrazol was administered, and the animal made an attempt to stand but was unable to do so. Respirations increased from 17 to 24 per minute. At 17 minutes postinduction the animal was standing and walking.

Trial No. 4 was an experimental trial utilizing VAD on chloral hydrate-magnesium sulfate anesthesia. Respirations ranged from 14 to 30 per minute. At 48 minutes postinduction 3.2 mg./kg. of VAD was administered, and standing occurred at 50 minutes postinduction. Tonic or clonic spasms did not occur in this trial.

Trial No. 5 was an experimental trial utilizing VAD following pentobarbital sodium anesthesia. Respirations ranged from 16 to 20 per minute. At 16

Graph 9. Standing time of the experimental and control trials with horse No. 11.



minutes postinduction 3.4 mg./kg. of VAD was diluted in 400 ml. of physiological saline and was given over a 4 minute period. At the end of the 4 minute period the animal was able to stand.

Trial No. 6 was an experimental trial utilizing pentylenetetrazol following chloral hydrate-magnesium sulfate anesthesia. Respirations ranged from 14 to 15 per minute. At 9 minutes postinduction 4.6 mg./kg. of pentylenetetrazol was given and the horse was standing in 50 seconds.

Trial No. 7 was a control trial with pentobarbital sodium induced anesthesia. The respirations ranged from 17 to 31 per minute. At 12 minutes postinduction an effort to stand was made; however, the horse was unable to stand until 22 minutes postinduction.

Trial No. 8 was a control trial with chloral hydrate-magnesium sulfate anesthesia. The animal did not reach a state of narcosis and since this was a control trial, additional anesthetic was not given.

GRAPH 9

Graph 9 is a comparison in graph form of the standing times of the anesthetic trials conducted on horse No. 11. Four of the trials involved pentobarbital sodium anesthesia and 4 involved chloral hydrate-magnesium sulfate induced anesthesia.

An initial dose of 7.5 mg./kg. of pentobarbital sodium was given on the first pentobarbital sodium trial and a state of surgical anesthesia was attained. On the second pentobarbital sodium trial 9.75 mg./kg. was required to produce a state of narcosis. On the third trial 9.75 mg./kg. produced only a state of sedation. Consequently, the dose of pentobarbital sodium was increased to 14.6 mg./kg., and a state of surgical anesthesia was attained. In the fourth trial 14.6 mg./kg. of pentobarbital sodium produced only a state

of sedation. Therefore, the dosage was increased to 18.0 mg./kg. in order to produce a state of narcosis.

Trial No. 1 utilized pentylenetetrazol following pentobarbital sodium anesthesia. Respirations ranged from 18 to 20 per minute. A state of surgical anesthesia was attained, and starting at 20 minutes postinduction a total of 12.5 mg./kg. of pentylenetetrazol was administered. The respiratory rate increased from 20 to 34 per minute. An attempt to stand was made, but it was 47 minutes postinduction before standing occurred.

Trial No. 2 was a control trial with chloral hydrate-magnesium sulfate induced anesthesia. Respirations ranged from 9 to 12 per minute. At 25 minutes postinduction the animal was able to attain a position of sternal recumbency. At 30 minutes postinduction the animal was able to stand but was incoordinated when walking.

Trial No. 3 utilized VAD following chloral hydrate-magnesium sulfate induced anesthesia. Respirations ranged from 16 to 16 per minute. At 16 minutes postinduction 7.5 mg./kg. of VAD was given over a 1 minute period. Clonic spasms occurred for 2 minutes following completion of administration of VAD. The animal was able to stand 21 minutes postinduction.

Trial No. 4 was a control trial with pentobarbital sodium induced anesthesia. In this trial it was necessary to increase the dosage from 7.5 mg./kg. to 9.75 mg./kg. to attain a state of narcosis. At 28 minutes postinduction the animal was able to attain a position of sternal recumbency. Standing occurred at 46 minutes postinduction.

Trial No. 5 utilized pentylenetetrazol on pentobarbital sodium induced anesthesia. The dosage was increased to 14.6 mg./kg. because the animal failed to reach a state of narcosis with the previously established dose of 9.75 mg./kg.

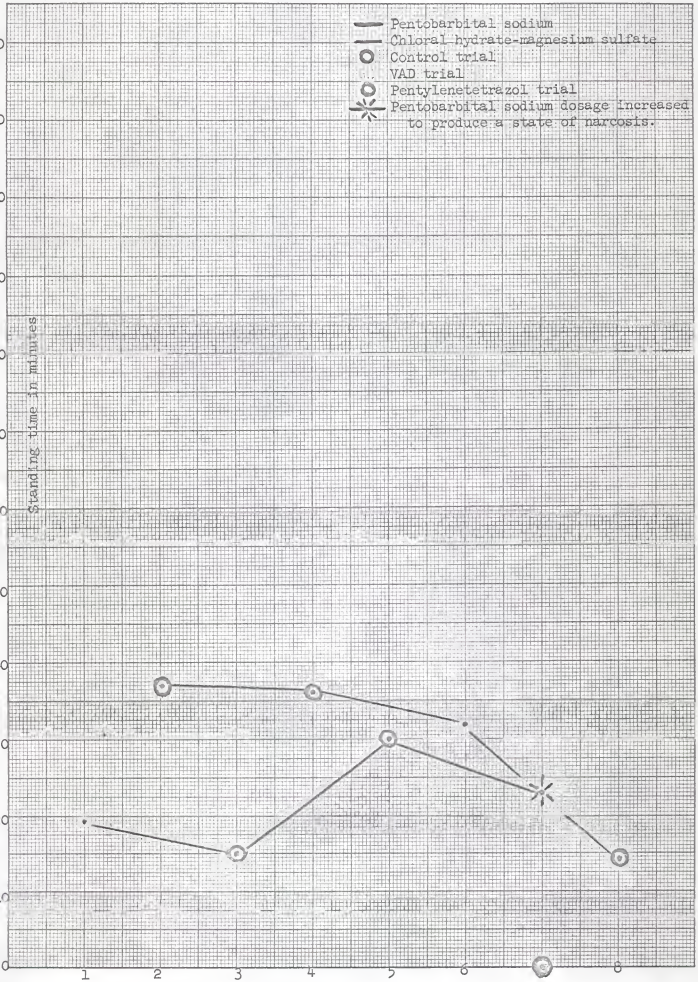
Surgical anesthesia was attained following administration of the increased dosage. The respiratory rate ranged from 10 to 13 per minute. At 106 minutes postinduction 10.0 mg./kg. of pentylenetetrazol was administered. At 113 minutes postinduction the patient was able to stand and walk.

Trial No. 6 was an experimental trial utilizing pentylenetetrazol following chloral hydrate-magnesium sulfate anesthesia. Respirations ranged from 12 to 16 per minute. At 10 minutes postinduction 7.5 mg./kg. of pentylenetetrazol was given, and the animal was standing in 45 seconds.

Trial No. 7 was a control trial with chloral hydrate-magnesium sulfate induced anesthesia. Respirations ranged from 12 to 14 per minute. At 11 minutes postinduction an attempt to stand was made, but the animal was unable to stand until 13 minutes postinduction.

Trial No. 8 utilized pentylenetetrazol following pentobarbital anesthesia. A dosage of 14.6 mg./kg. was given, and only a state of sedation was attained; consequently, dosage was increased to 18.0 mg./kg. in order to produce a state of narcosis. During this trial a total of 69.0 mg./kg. was administered over an 86 minute period to enable to cast to be placed on a fracture of the third metacarpal of the left foreleg. Respirations ranged from 6 to 10 per minute during the narcosis stage. A total of 39 mg./kg. of pentylenetetrazol was administered over a 30 minute period starting at 160 minutes postinduction. Respirations increased from 10 to 26 per minute. The animal was able to stand at 190 minutes postinduction.

Graph 10. Standing time of the experimental and control trials with horse No. 12.



GRAPH 10

Graph 10 shows a comparison of the standing times of the experimental trials conducted on horse No. 12. The graph is constructed in the same manner as graph 3.

A constant dosage was used throughout the 4 chloral hydrate-magnesium sulfate induced anesthesia trials. In the first 3 trials utilizing pentobarbital sodium anesthesia a constant dosage of 12.3 mg./kg. was administered, but the fourth time this drug was used it was necessary to increase the dosage to 15.6 mg./kg. in order to produce a state of narcosis.

Trial No. 1 utilized VAD following pentobarbital sodium induced anesthesia. Respirations ranged from 14 to 16 per minute. At 19 minutes postinduction 1.0 mg./kg. of VAD was administered, and the animal was standing in 1 minute.

Trial No. 2 was a control trial in which chloral hydrate-magnesium sulfate was used as the anesthetic agent. Respirations ranged from 12 to 16 per minute during the anesthetic state. At 20 minutes postinduction the animal was able to lift its head. At 37 minutes postinduction the animal was standing.

Trial No. 3 utilized pentylenetetrazol following pentobarbital sodium induced anesthesia. Respirations ranged from 14 to 16 per minute. At 14 minutes postinduction 4.2 mg./kg. of pentylenetetrazol was administered, and the animal was standing in 40 seconds.

Trial No. 4 utilized pentylenetetrazol following chloral hydrate-magnesium sulfate induced anesthesia. Respirations ranged from 12 to 19 per minute. At 34 minutes postinduction 4.2 mg./kg. of pentylenetetrazol was given, and the patient was standing in 2 minutes.

Trial No. 5 was a control trial involving pentobarbital sodium anesthesia. Respirations ranged from 14 to 27 per minute. At 13 minutes postinduction the animal was able to attain a position of sternal recumbency, but it was unable to stand until 30 minutes postinduction.

Trial No. 6 was an experimental trial utilizing VAD following chloral hydrate-magnesium sulfate induced anesthesia. Respirations ranged from 16 to 20 per minute. Starting at 10 minutes postinduction 4.2 mg./kg. of VAD was given over a 2 minute period. Some tonic and clonic spasms occurred for a period of 1 minute and standing occurred at 34 minutes postinduction.

Trial No. 7 was a control trial involving pentobarbital sodium anesthesia. It was necessary to increase the dosage from 12.3 to 15.6 mg./kg. to attain a state of narcosis. A standing position was attained at 23 minutes post-induction.

Trial No. 8 was a control trial involving chloral hydrate-magnesium sulfate induced anesthesia. Respirations ranged from 18 to 20 per minute. Standing occurred at 14 minutes postinduction.

DISCUSSION

The use of VAD or pentylenetetrazol as arousal agents in the equine species has not been reported, consequently information concerning their most effective dosage, rate of administration, and the level of anesthesia at which time the most desirable results would be attained was not available. Therefore, the dosage, rate of administration, and level of anesthesia at which time the arousal agents were administered were varied in an attempt to establish the dose, rate of administration, and the level of anesthesia at which to administer the drugs.

In considering the effectiveness of vanillic acid diethylamide and pentylenetetrazol as arousal agents, the increased tolerance which developed to the anesthetic agents makes it difficult to make precise comparisons. Even the standing times of the control trials with these agents cannot be accurately compared with the experimental trials due to increased tolerance.

According to Sollmann (1957) tolerance may be due to nonabsorption, to rapid elimination, to neutralization or destruction of the poison, or to anatomic perculiarities. Tolerance is rarely absolute, so it is incorrect to speak of "immunity". It may be congenital or may be developed by repeated administration of the poison. Tolerance to habit-producing drugs is largely psychic: the nervous centers learn to modify their reactions so as to adapt them to the drug environment.

Dogs become tolerant to several barbiturates as determined by the reduction in sleeping time of a given and frequently repeated dose. A cross-tolerance for all barbiturates occurs with a tolerance developed to one barbiturate. In a dog with tolerance to a sleep-inducing dose of a barbiturate, there is no change in the LD50 dose. Tolerance is soon lost by withdrawal of the drug (Jones, 1957).

The increased tolerance to the anesthetic agents in these studies indicate that the body can adjust to repeated administration of these agents. This increased tolerance appears to be due to the nervous system adjusting to the anesthetic agents.

In 11 of the 18 trials where VAD was utilized as an arousal agent, there were tonic and clonic spasms. In comparing the trials where spasms occurred to those where spasms did not occur, it appears that additional work needs to be done in the area of dosage and rate of administration. Although there is some direct relationship between the dosage, the spasms and the rate of administration, the correlation between high dosage and rapid administration was not consistent. In certain instances, higher doses that were given rapidly did not produce spasms. Conversely, certain of the trials involving low dosages and some of the trials where the dosage was given slowly resulted in tonic and clonic spasms.

In those patients under surgical anesthesia, the arousal actions were less pronounced. An increase in the respiratory rate was noted and slight signs of arousal were observed in these trials. The analeptic effect usually lasted for 10 minutes reaching its peak 3 minutes after the injection. The respiratory rate was usually back down to the rate before the VAD was given by 10 minutes postinjection.

In those trials where the animal was able to stand following administration of VAD, relapse to surgical anesthesia or narcosis was not observed.

Of the experimental trials with VAD, there were tonic and clonic spasms in 11 of the 18 trials. Nine of the 18 trials were chloral hydrate-magnesium sulfate and 9 with pentobarbital sodium. Spasms occurred in 66.7 per cent of the chloral hydrate-magnesium sulfate trials and in 55.5 per cent of the pentobarbital sodium trials.

In comparing the trials where spasms occurred to those where they did not occur, the dosage, rapidity of injection and depth of anesthesia are factors which must be considered. Of those trials where spasms occurred in chloral hydrate-magnesium sulfate anesthesia, the dosage ranged from 4.2 to 7.7 mg./kg. The 4.2 mg./kg. was given over a 2 minute period and the 7.7 mg./kg. over a 1 minute period. The longest period of injection of those trials where spasms occurred was 15 minutes. In this case 6.4 mg./kg. of VAD was diluted in 450 ml. of physiological saline and the mixture was given slowly over a 15 minute period. In the 3 trials where spasms did not occur, the dosage range was from 3.2 to 5.4 mg./kg. The 3.2 mg./kg. was given over a 1 minute period and the 5.4 mg./kg. was given over a 4 minute period.

Of those trials where spasms occurred in pentobarbital sodium anesthesia, the dosage ranged from 1.0 to 9.3 mg./kg. The 1.0 mg./kg. was given over a 1 minute period and the 9.3 mg./kg. over a 2 minute period. In the 4 trials where spasms did not occur the dosage ranged from 3.2 to 6.0 mg./kg. The 3.2 mg./kg. was given over a 3 minute period and the 6.0 mg./kg. over an 18 minute period.

The doses and rate of administration utilized in the trials with pentylenetetrazol did not result in tonic and clonic spasms such as were observed in the VAD trials. The arousal actions were pronounced in animals that were showing signs of recovery from the anesthetic agents. The animal was usually able to stand within 1 minute following administration of pentylenetetrazol if the patient was able to raise its head prior to the injection of the pentylenetetrazol.

In those trials where the patient was in a state of surgical anesthesia at the time of administration of the arousal drug, pentylenetetrazol would

lighten the state of anesthesia. But at the doses employed standing did not occur immediately. In those trials where the animal was able to regain its feet following administration of pentylenetetrazol, evidence of postpentylenetetrazol depression such as the patient slipping back into a state of narcosis was not observed.

In those trials where the animal was in a state of surgical anesthesia and the respiratory rate was depressed, an analeptic action was noted. This action usually lasted for 10 minutes reaching a maximum at about 3 minutes postinjection. The arousal effect in these cases was characterized by eye blinking, swallowing reflexes, and in some cases by the animal liftings its head. In such cases the patient usually regressed back into the approximately same state of anesthesia that it was before the administration of pentylenetetrazol. These animals would generally seem to recover at about the same rate as the controls unless additional pentylenetetrazol was administered as the animal was starting to show signs of recovery.

Based on the observations in these trials it would appear that pentylenetetrazol has several advantages over vanillic acid diethylamide at the dosages and rates of administration that were employed in this study. The arousal times were generally shorter and nervous excitement was not observed when pentylenetetrazol was utilized as the arousal agent. With VAD there were spasms in 11 of the 18 trials.

In horses under surgical anesthesia neither of the agents employed were able to arouse the patient to the point where he could stand. Both VAD and pentylenetetrazol were effective as analeptic agents. The duration of action was approximately the same for both of the agents.

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LITERATURE CITED

Adriani, J.
Chemistry of Anesthesia. Charles C. Thomas Publisher, Springfield, Illinois. 1956.

Alfredson, B. V.
Notes on Pentobarbital-Metrazol Antagonism. M. S. C. Vet., Spring 1941.

Anderton, J. L., Cowie, J. F., Harris, E. A., and Sleet, R. A.
Effect of Ethamivan (Vanillic Acid Diethylamide) on the Respiratory Response of Healthy Young Men to Carbon Dioxide, in the Absence of Hypoxia. Brit. J. Pharmacol. 19:142-152, 1962.

Antelyes, J.
Evaluation of a Respiratory Stimulant and Arousal Drug. Small Animal Clinician. 2:12:688-692. 1962.

Arthur, G. H., Vaughn, L. C. and Yeats, J. J.
Pentobarbital Sodium Sedation in the Horse. Vet. Rec. 65:409-410. 1953.

Barlow, F. R.
Metrazol in Small Animal Surgery, Jour. A.V.M.A 108:232. 1946.

Bemis, H. E., Guard, W. F., Covault, C. H.
Anesthesia, General and Local, Jour. A.V.M.A 17:413. 1924.

Bernstine, M. L., and Moskal, J. P.
Effect of Vanillic Diethylamid (Vandid) on Arousal and Awakening Time Following Thiopental Anesthesia. Anesthesiology. Jan-Feb. 1960.

Cole, G. W., Marks, A., and Baum, G. L.
Barbiturate Poisoning. Jour. A.M.A. 174:156-157. 1960.

Danks, A. G.
Anesthesia in Horses and Swine. Cornell Vet. 33:344. 1943.

Esplin, D. W., Woodbury, D. W., and Goodman, L. S.
Distribution, Fate and Excretion of Pentylenetetrazol. Fed. Proc. 13:352 (Mar) 1954.

Ford, E. J. H. Some Observations on the Use of Thiopenton in Large Animals. Vet. Rec. 63:636. 1951.

Fowler, G. R.
General Anesthesia in Large Animals. Jour. A.V.M.A. 96:210. 1940.

Fulton, J. F. and Keller, A. D.
The Sign of Babinski--A study of Cortical Dominance in Primates. Charles C. Thomas, Baltimore. 1932.

Frank, E. R.
Veterinary Surgery Notes, Rev. Ed. Burgess Pub. Co., Minneapolis, Minnesota. 1959.

Gilmour, J. P.
Chloroform. Quart. J. Pharm. and Pharmacol. 7:440. 1934.

Goffinet, P.
Abstract: Am. de Vet. Med. Jour. A.V.M.A. 94:448. 1939.

Goodman, L., and Gilman, A.
The Pharmacologic Basis of Therapy. The MacMillan Company, New York, New York, 813. 1955.

Groves, L. W.
Equine Anesthesia. Jour. A.V.M.A. 119:50. 1951.

Jones, E. W.
Equine Anesthesia--Maintenance by Inhalation Techniques. Jour. A.V.M.A. 139:785-790. 1961.

Jones, E. W., Johnson, L. and Heinze, D. C.
Thiopental Sodium Anesthesia in the Horse--A Rapid Injection Technique. Jour. A.V.M.A. 137:119-122. 1960.

Jones, L. M.
Veterinary Pharmacology and Therapeutics. Second Edition. Iowa State University Press, Ames, Iowa. 1957.

Krantz, J. C. and Carr, J. C.
Pharmacologic Principles of Medical Practice, Fifth Edition. The Williams and Wilkins Company. Baltimore. 1961.

Lumb, W. V.
Small Animal Anesthesia. Lea and Febiger, Philadelphia, Pa 1963.

Mackay, F. H., and Cooper, L. R.
Study of Hypnotic Activity of Chloral Hydrate. J. Pharmacol. and Exper. Therap. 135:271-274. 1962.

Millenbruck, E. W., and Wallinga, M. H.
A Newly Developed Anesthetic for Horses. Jour. A.V.M.A. 108:148. 1946.

Millenbruck, E. W.
A Newly Developed Anesthetic for Large Animals. Jour. A.V.M.A. 112:345. 1948.

Miller, M. J., Hand, M. B., and Crellin, J. A.
Pharmacologic Effects of Intravenous Vanillic Acid Diethylamide in Man. Clinical Pharmacology and Therapeutics. 2:5:689-691. 1961.

Pleuger, C. A.
The Problems of Feline Anesthesia. Jour. A.V.M.A. 51:39, July 1942.

Romagnoli, A., and Diamond, M. J.
Some Trials with Vanillic Diethylamide: A New Analeptic. Can. Anaes. Soc. J. 8:6:551-555. 1961.

Schmidt, K. F.
Uber "Cardiazol" ein in Wasseriger Losung subcutan injiziebares neues Analepticum. Klin. Wschr., 4:1678. 1925.

Sollman, T.
A Manual of Pharmacology, 7th Ed. W. B. Saunders Co., Philadephia, Pa. 631, 675, and 743. 1958. pg. 39. 1957.

Tartler, O. P.
Diss. Giessen, 1929. Quoted from F. Hildebrandt: Pentamethylenetetrazol (Metrazol) in Handbuch der Experimentellen Pharmakol., 113:257. 1926.

Tavernor, W. D.
Equine Anesthesia. Vet. Rec. 73:545. 1961.

Wright, J. G.
Veterinary Anesthesia, 4th Ed. Tindall and Cox, London, England. 1957.

A COMPARISON OF VANILLIC ACID DIETHYLAMIDE AND PENTYLENETETRAZOL AS AROUSAL AGENTS IN THE EQUINE SPECIES

by

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The need for an effective arousal agent in the equine species has been generally recognized particularly because of the variation in response to an intravenous anesthetic in this species. The intravenous anesthetics are commonly used by the equine specialist due to the low cost of the anesthetic, ease of administration, and minimal requirement for professional assistants, however the unpredictable and often prolonged recovery time has kept many general practitioners from using intravenous anesthesia in the equine species.

A comparative evaluation of vanillic acid diethylamide (VAD) and pentylenetetrazol was undertaken with the possibility that either of these might greatly reduce the recovery time following intravenous anesthesia and thus increase the practicality of this type of anesthesia in all types of practice.

Eight horses of varying ages, weights, and breeds were utilized in the study. Four of the animals were females and 4 were castrated males.

Control trials consisted of anesthetizing each animal with pentobarbital sodium or chloral hydrate-magnesium sulfate solution and allowing the animals to recover normally. Experimental trials consisted of anesthetizing each animal with either pentobarbital sodium or chloral hydrate-magnesium sulfate and then administering pentylenetetrazol or VAD.

Because of the difference in response to the anesthetic agents employed, varying doses of pentobarbital sodium and chloral hydrate-magnesium sulfate were utilized. The dose of the anesthetic agent required to produce narcosis was initially determined in the first trial with each of the anesthetic agents. Subsequently this dose was administered in each of the succeeding trials with that agent. When the animal had developed tolerance to the anesthetic agent so that a state of narcosis was not attained, then the dosage was increased to provide the state of narcosis necessary to evaluate the arousal agent.

Lack of reports in the literature concerning dosages, rates of administration, and the ideal level of anesthesia at which time to administer the arousal agents, made it necessary to utilize various dosages and rates of administration within the experimental procedures.

Tolerance to pentobarbital sodium was demonstrated in 8 animals and tolerance to chloral hydrate-magnesium sulfate was demonstrated in 5 animals. The use of pentylenetetrazol as an arousal agent in those animals under light narcosis was particularly effective in this study. Vanillic acid diethylamide was not as an effective arousal agent as pentylenetetrazol at the doses and rates of administration that were utilized in this study. Both VAD and pentylenetetrazol were effective analeptic agents when utilized in patients that were in a state of surgical anesthesia. Neither VAD or pentylenetetrazol was effective in arousing the patient to a point that it could stand within a short period of time if the arousal agent was given while the animal was in a state of surgical anesthesia.

Mild to severe spasms occurred in 61.1 per cent of the trials where VAD was employed as the arousal agent. It was difficult to correlate the dose and/or rate of administration of the drug in those trials where spasms occurred.

The results obtained in this experimental study indicated that pentylenetetrazol was apparently superior to vanillic acid diethylamide as an arousal agent in the equine species whereas both drugs were nearly equal in their effectiveness as respiratory analeptics in those animals in a state of surgical anesthesia.