SOME RESPIRATORY STIMULANTS IN DEEPLY BARBITALIZED DOGS

Thesis for the Degree of M. S.

MICHIGAN STATE UNIVERSITY

Chaturbhuj Singh Sisodia

1960

SOME RESPIRATORY STIMULANTS IN DEEPLY BARBITALIZED DOGS

By

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A THESIS

Submitted to the College of Veterinary Medicine
of Michigan State University in partial
fulfillment of the requirements
for the degree of

MASTER OF SCIENCE

Department of Physiology and Pharmacology

1960

Dedicated to

my respected and loving uncle,

Major Hem Singh ji.

ACKNOWLEDGMENTS

The author wishes to express his sincerest gratitude to Doctor Clyde F. Cairy, Professor of Physiology and Pharmacology, for his helpful guidance throughout the course of this work, for providing facilities in conducting this work and for his help and a assistance in the preparation of this manuscript.

He extends his sincere appreciation to Doctor B. V. Alfredson, Head of the Department of Physiology and Pharmacology, for his interest and encouragement; and to Doctor Robert M. Herbst, Professor of Chemistry, for his valuable suggestions.

He is also grateful to the other members of his guidance committee: Doctor William D. Collings, Professor of Physiology and Pharmacology and Doctor Raymond F. Johnston, Associate Professor of Physiology and Pharmacology.

Thanks are due to Doctor Achjani Almakusuma and Doctor V. M. Ramaswamy for their assistance in the preparation of experimental animals and also to my other colleagues who contributed in making my stay in this university a pleasant experience.

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INTRODUCTION

In this era of increasing population, diseases, injuries, worries and excitation, barbiturates are finding a growing use as hypnotics, narcotics and anesthetics. The more widely a drug is handled for such delicate purposes, the more are the chances of accidents by its deliberate or accidental improper use and overdosage.

The increasing popularity of barbiturates as suicidal agents has created a world-wide problem. And over the past decade the amount of barbiturate used on both sides of the Atlantic has more than trebled, while the incidence of the barbiturate coma has increased fivefold (Nilsson, 1951; Locket and Angus, 1952; Clemmessen, 1954; Goldstein, 1947; Koppanyi and Fezekas, 1950, 1952, 1954; Moller, 1954; Lancet, 1951, 1953; Goodman and Gilman, 1947).

Analeptics are CNS stimulants employed to counteract such CNS depressants as barbiturates. Some workers do not favor their use on the grounds that the convulsions they produce may cause irreparable damage to the brain through anoxia by increasing the cerebral oxygen demand in excess of the available oxygen supply. Others, who recommend their use, condemn this objection by the fact that barbiturates have a protective effect against anoxia (Miller and Miller, 1956) and state that analeptics by their awakening effects and respiratory and cardio-vascular stimulation really can save the patient against barbiturates.

There are many other advantages of analeptic therapy in barbiturate poisoning--e. g. prolonged endotracheal intubation is not needed, the immediate and delayed risk to the patient's life is lessened, the cost of treatment which, when symptomatic may require many hours of close attention by medical and nursing staff, is decreased, and the differential diagnosis of barbiturate intoxication from other conditions may be an aid in planning further therapy for the patient.

With the idea that two analeptics if used together may overcome the shortcomings of each other to a certain extent, thus making the combination better than its components, the author has attempted to determine the effects on respiration of all possible combinations of picrotoxin, pentylenetetrazol, amphetamine, methetharimide and metaraminol bitartrate in pairs and also of metaraminol bitartrate alone in deeply pentobarbitalized dogs. Such work on these individual drugs alone has previously been done in this laboratory (Leash and Cairy). Amphetamine and metaraminol bitartrate have been selected for such combinations also because of their cardiovascular effects. As suggested by Weaver and Bunde (1960) they may prove useful in the clinic, since they antagonize barbiturate effects on the cardiovascular system as well as the respiratory system.

CHAPTER I

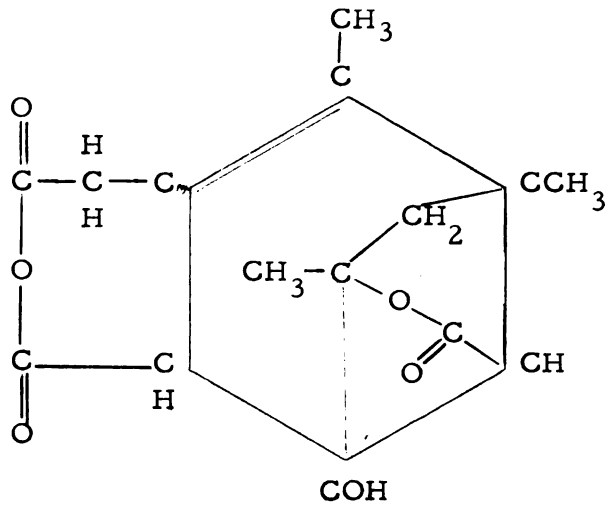
LITERATURE REVIEW

PICROTOXIN

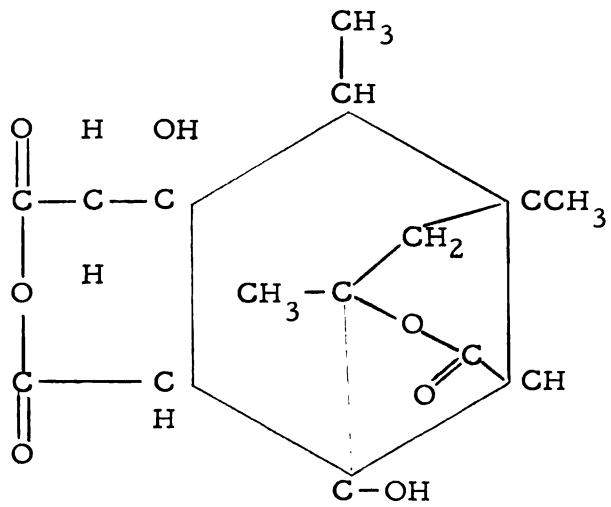
Picrotoxin in 1812 was first isolated by Boulay from Cacculus indicus called "fish berries." In 1847 Tschudi expressed the opinion that it might be a suitable antagonist to morphine. In 1875 J. Crichton Browne suggested its use in chloral hydrate poisoning. His observations were confirmed by a number of investigators both as to the life saving and awakening effects of picrotoxin in chloral hydrate and paraldehyde anesthesia.

Maloney, Fitch and Tatum (1931) and Maloney and Tatum (1932) were apparently the first to test the antidotal efficacy of picrotoxin in experimental barbiturate poisoning. They found that picrotoxin shortens the recovery from barbiturate anesthesia and that it protects animals receiving doses higher than the LD_{50} of the various barbiturates. Koppanyi (1936) and his associates explored the limits of the antidotal efficacy of picrotoxin in poisoning with barbiturates, determined the component factors of the antidotal mechanism and provided a rational explanation of both the awakening and the life saving effects in experimental barbiturate intoxication. They also introduced it for treatment of human barbiturate poisoning. Few, if any, critical or adverse reports were published and subsequently picrotoxin was introduced into the United States Pharmacopoeia.

Chemically picrotoxin is a neutral principle with the formula $C_{30}H_{34}O_{13}$. On boiling an aqueous solution it is readily hydrolised into its components Picrotoxinin and Picrotin which recombine upon cooling. Picrotoxinin and picrotin are present nearly in equal parts, both are closely allied chemically and have identical action but picrotoxinin acts far stronger.



Picrotoxinin



Picrotin

Picrotoxin is a powerful CNS stimulant. It is said to exert its action more on the midbrain and the medulla than on the cortex and it is only with higher doses that the spinal cord is affected. Higher centers of integration are first stimulated and then depressed. Higher doses of picrotoxin cause convulsions.

In the medulla, the respiratory, vomiting and vasomotor centers are quite obviously stimulated. Respiratory stimulation is more marked if the respiratory center has been depressed by some CNS depressant. In normal subjects any marked respiratory stimulation is seen only with convulsive doses. Stimulation of the vomiting center results in increased salivation and sometimes emesis. Blood pressure very often goes up due to stimulation of vasomotor center but falls 3-8 seconds before convulsions. Heart rate may be slowed or even cease for a while by direct vagal stimulation or even reflexly due to high blood pressure. Later on heart rate may go up due to stimulation of accelerator center or paralysis and fatigue of vagal center and its nerve endings. Picrotoxin also shows a specific stimulation effect on all the centers of the parasympathetic nerves known.

Location of Picrotoxin convulsions--It has been argued that the convulsions originate in the midbrain with minimal doses, that larger doses involve also the medulla and very large doses extend to the spinal cord too. Convulsions are unaltered by removal of the cerebral hemispheres or even by transections below the optic thalami, but with section below the medulla they either disappear or become similar to those of

strychnine poisoning. Direct injection of picrotoxin into hypothalamus causes autonomic and emotional stimulation. Although the convulsions appear to occur spontaneously in cycles they are prevented by removal of skin in frogs showing that they involve the intactness of sensory impressions. Picrotoxin has a latent period of 8-10 minutes sometimes even more between the intravenous injection and the onset of its action and convulsions may start as long as 30 minutes after injection.

Depressing effects of picrotoxin--Picrotoxin in addition to its stimulant action produces a sort of depression in rats and rabbits. This depression is manifested in rabbits by loss of placement reaction which indicates that cortical function is impaired. It appears with doses of picrotoxin which approach but don't reach convulsive levels.

With convulsive doses of this drug the depression appears before the convulsive attack and lasts for a considerable time afterwards and is apparently independent of the convulsions.

Activity studies in rats by Dille and Hazleton (1939) showed a decrease during the first hour after the administration of convulsive doses of picrotoxin. This decrease is probably due to the cortical depression. When used as an analeptic there is a critical dose level with picrotoxin. Below this level there is shortening of recovery time of the cortical placement reaction, but above this level there is prolongation of the recovery of these reactions. In all doses of picrotoxin there is decrease in the recovery time of the "righting reflex."

Picrotoxin stimulates sweating by stimulating the spinal centers. It decreases body temperature without producing convulsions and may have its site of action in the hypothetical center inhibiting heat formation and this center is to be regarded as parasympathetic (Meyer and Gottleib translated by Handerson).

Fate and excretion--Picrotoxin disappears in 1-2 hours from blood, liver and muscles (Duff and Dille, 1939). Less than 10 percent of convulsive dose in rabbit is excreted by urine (Dille, 1938). Christoni (1912) claimed that the picrotoxin is excreted partly unchanged and that the picrotoxinin is decomposed

Picrotoxin barbiturate antagonism--Specific antagonism between picrotoxin and barbiturates has been shown by many workers. Goodman and Gilman describe picrotoxin as "one of the most effective of the CNS stimulants" in barbiturate poisoning. It reinstates adequate respiration and greatly lessens the degree of anesthesia. A very rational explanation for this antagonism against barbiturates has been given by Koppanyi, Linger and Dille (1936) under the following headings:

1. Awakening effects--Cortical antagonism. They showed this by abolishing the excitability of motor cortex in some dogs by barbiturates and then making it excitable again by appropriate doses of picrotoxin. They also showed that previous or simultaneous administration of an antidote like picrotoxin may prevent or lessen the depth of pentobarbital narcosis, and that the action of the analeptic which is responsible

for its denarcotizing effect is not responsible for its convulsive effects as an animal, though comatose under barbiturate depression, may still show convulsions with picrotoxin.

A barbiturate poisoned animal awakened by picrotoxin, however, may go back in deep depression again after the analeptic effect of picrotoxin ceases but may be awakened repeatedly by appropriate doses of the analeptic. This indicates that it does not actually destroy the barbiturate; instead antagonizes it only physiologically.

2. Medullary effects--Picrotoxin directly stimulates the depressed medullary centers e.g. respiratory center and vasomotor center to increase ventillation and blood pressure. Denarcotizing effect of the drug also seems to be an important factor in stimulating these centers indirectly.

It was also shown (by Krantz et al., 1937) that the antidotal action of picrotoxin is not associated with increased oxygen uptake of brain tissue in general or brain tissue rich in vital centers.

The fact that picrotoxin occasionally fails to raise the blood pressure of barbitalized animal may be explained by the assumption that the vasodepressant action of barbiturates is partly peripheral and picrotoxin is apparently only effective against the blood pressure effects of central origin.

3. Effect on body temperature--Picrotoxin by many workers has been said to lower body temperature while the barbiturate also

gradually but markedly lowers body temperature. But picrotoxin when used as an analeptic in life saving doses against barbiturate depression raises the temperature back towards normal, probably by: (a) direct stimulation of heat producing center, (b) direct stimulation of heat regulating mechanism, (c) improving peripheral circulation.

4. Effect of picrotoxin on barbiturate destruction in body--There is no chemical reaction between picrotoxin and barbiturates in vitro nor is there any chemical antagonism between them in vivo, and in most cases studied, the concentration of barbiturates in the animal awakened by picrotoxin was the same as in untreated depressed animals. Thus picrotoxin does not augment the destruction of barbiturates in the animal body, but in some cases the awakened animals, due to their better physiological condition, may be able to destroy larger amounts of hypnotics.

Koppanyi, Lineger and Dille (1936) also showed that picrotoxin has only a limited antagonistic effect against barbiturates and that barbiturates can antagonize many more LD_{50}'s of picrotoxin than picrotoxin can of barbiturates. This makes one to conclude that barbiturates act on a more extensive area in the CNS than does picrotoxin, and that the two are not perfect antagonists of each other in the true sense. Thus when barbiturates and picrotoxin are given together, what results is not a direct reversal of the depressed state but a combined form of poisoning by barbiturates and picrotoxin with a mixture

of depression and stimulation from which, within a given range of doses, the animal ultimately recovers. Micks (1950) goes still further to say that the production of convulsions during attempts to revive a patient from narcotic poisoning constitutes a serious mistake in the treatment, for a convulsion is followed by a period of cerebral depression which in deeply narcotized patients may be fatal. Billow (1950) says, "picrotoxin has a narrow margin of safety and still remains a drug to be used with great caution and clinical acumen. Particularly disturbing is the fact that the patient is often in a state of coma and is having convulsions." This is because the action of picrotoxin on the cerebral cortex is less than on the midbrain, medulla and the spinal cord.

Picrotoxin against short and long acting barbiturates--The short acting barbiturates tend to cause death by respiratory paralysis with above minimal lethal doses, while long acting barbiturates with such doses cause prolonged narcosis ending in pulmonary congestion, other complications and death, while the anesthesia level is very low even just before death, in comparison to short acting barbiturates.

Picrotoxin effects a comparatively speedy recovery from poisoning by short acting barbiturates when they are given in sublethal doses, whereas recovery is considerably delayed in cases of sublethal poisoning with long acting barbiturates.

Effects of short acting barbiturates are quick and intense and so the antidote is given intravenously, while the effects of long

acting barbiturates are less intense throughout and slower in onset, and so the antidote is given in numerous small doses by subcutaneous or intramuscular routes. The margin between therapeutic and convulsant dose of the antidote is narrower due to low level of anesthesia produced by these long acting barbiturates.

Thus picrotoxin can antagonize higher doses of short acting barbiturates than long acting ones. In sublethal doses of long acting barbiturates picrotoxin shortens the recovery time. Against lethal doses within certain limits it effects a cure, and against doses beyond these limits of hopeful therapeutics, it only prolongs the life of the patient.

Rate of absorption and excretion of picrotoxin is quite rapid, and so small and repeated doses of picrotoxin are advised in antagonizing the depression of long acting barbiturates.

Picrotoxin against other CNS depressants--In general picrotoxin is not so specifically effective against other CNS depressants as against barbiturates. It is very effective in reinstating respiration which has failed from overdose of chlorbutanol, paraldehyde or "avertin fluid " It is less effective against overdose with urethane and useless against ethyl alcohol depression.

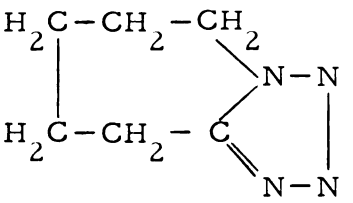
Picrotoxin has little awakening effect but antagonizes the circulatory and respiratory depression in morphine narcosis in dogs and also prevents further circulatory and respiratory depression by

subsequent I/V doses of morphine. Picrotoxin acts synergistically with morphine to induce convulsions with even smaller doses and so instead decreases its MLD.

It also raises blood pressure and stimulates respiration in depression produced by sodium bromide.

PENTYLENETETRAZOL

Chemically--Pentamethylene tetrazol



Proprietary names--Metrazol, Cardiazol, Phronazol, Hexazol, Azoman etc.

Pharmacological actions--Pentylenetetrazol is a fairly potent CNS stimulant. Its actions are highly complex and apparently occur at all levels of the cerebrospinal axis. It can stimulate both the motor as well as sensory apparatus of the nervous system in the body.

It stimulates the medulla and so the respiratory center to increase ventilation. Its medullary stimulation effect is direct as it exists even after complete denervation of the carotid sinus and carotid body. It produces significant respiratory stimulation in normal animals only with doses approaching the convulsive dose, but in anesthetized animals the subconvulsive therapeutic doses are quite effective. It also stimulates vagal and vasomotor centers which counteract each other's effects ultimately producing little effect on blood pressure. Sometimes the vagal effect is more potent and causes bradycardia and hypotension. In subjects with hypotension due to CNS depression it acts as an antagonist and tends to raise the blood pressure to normal. It increases cerebral blood flow by dilating the cerebral blood vessels.

Pentylenetetrazol increases reflex activity of the spinal cord. The effect is more marked on a chemically depressed spinal cord. Koll (1937) noted that maximum reflex activity of the spinal cord obtained by pentylenetetrazol could be further increased by strychnine and vice versa. This shows that the areas of action of both the drugs do not exactly coincide with each other.

Pentylenetetrazol exerts characteristic effects on electroencephalograms. With large doses it causes convulsions. It is seen that the lower is the level of transection of the brain, the higher is the convulsive dose. Character of the convulsions indicates their origin in the midbrain. They occur quite typically in cats and rabbits whose hemispheres have been removed. Direct injection of pentylenetetrazol into the hypothalamus causes autonomic stimulation, cyclodilation, piloerection, urination, defecation, marked emotional excitement and increased response to faradic stimulation of the region (Masserman, 1938). Pentylenetetrazol convulsions are accompanied by central excitation of both divisions of the autonomic nervous system, especially the sympathetic and this occurs also if the convulsions are prevented by curare (Gellhorn and Darrow, 1939).

During convulsions in rabbits, acidosis occurs (Dietrich and Ebster, 1928) and the blood sugar rises (Kastein et al., 1937). Convulsive response of the animal is decreased by repeated injections of Metrazol, by starvation, by dehydration and by calcium deficiency;

it is increased by water retention (Kastein, 1937). During convulsions the brain metabolism is diminished by anoxia (Himwich et al., 1939), and its lactic acid may be increased (Stone, 1938).

Depressing effect of pentylenetetrazol--Convulsions are succeeded by depression but no depression occurs with subconvulsive doses of pentylenetetrazol as occurs with picrotoxin (Dille and Hazelton, 1939). Like picrotoxin, when used as an analeptic, pentylenetetrazol too shows a critical dose level above which there is prolongation of recovery of the cortical placement reactions but decrease in recovery of the righting reflex. Dose levels immediately below this decrease the recovery of both these responses, but still lower doses prolong their recovery (Dille and Hazelton, 1939).

Pentylenetetrazol also stimulates the neuromuscular junctions (Eyzaguirre and Lilienthal, 1949). Pentylenetetrazol has little direct effect on heart or blood vessels and has no significant effect on coronary flow too. It may cause splanchnic and cerebral vasodilation. During convulsions the arterial pressure may be considerably raised due to skeletal muscle contractions. Conduction disturbances, e. g. sinus arrhythmia, alternation of pacemaker between S. A. and A. V. nodes and rarely heart block, occur but these have been attributed to the central effects of the drugs on autonomic nuclei.

Fate and Excretion--Goodman and Gilman are of the opinion that pentylenetetrazol is absorbed rapidly from the blood and stored temporarily

in the liver as an unidentified compound. Esplin et al. (1954) say that 75 percent of the pentylenetetrazol absorbed is excreted in the urine as such

An entirely different view is held by some other workers. Tatum, Kozelka and Nelson (1938) state that pentylenetetrazol leaves the blood rapidly after intravenous injection so as to establish practically equal concentrations in muscle, brain, liver and blood. Very little is excreted with urine and bile and only a part can be demonstrated in feces of guinea pigs by bioassay but not chemically (Hinsberg, 1939).

Pentylenetetrazol-barbiturate antagonism--Pentylenetetrazol is one of the most popular analeptics against barbiturates. Like picrotoxin it exerts a denarcotizing effect (Koppanyi et al., 1936), a "definite respiratory stimulant effect" (Alfredson, 1941) and a circulatory stimulant effect on the patient. A remarkable study on this antagonism has been done by Fezekas, Goldbaum, Koppanyi and Shea (1956) on human volunteers. They showed that Metrazol (up to 6000 mg) in a definite proportion of 3:1 with pentobarbital sodium (up to 2000 mg) afforded a significant protection against the depressant effects of the latter. These doses of both were normally highly toxic alone. Emesis occurred in 7 out of 10 subjects indicating denarcotizing of the vomiting mechanism. Frank convulsions or anesthesia were not observed. Absorption from gastro-intestinal tract of pentobarbital was much quicker in the control group (pentobarbital alone) than it was in the experimental group

(combination). A blood level of 12 mg per liter caused marked depression in the control group but still higher levels could not produce such marked depression in the experimental group. Pentylenetetrazol appeared to be more specific against phenobarbital than pentobarbital.

Pentylenetetrazol had no effect on removal of pentobarbital from blood. There are three suggested mechanisms by which pentylenetetrazol may exert its protective effects against barbiturates:

1. Physiological antagonism--This phenomenon is not well understood yet. Torda (1954) believes that pentylenetetrazol induces central stimulation by increasing the acetylcholine content of brain along with another unknown process. What ever the phenomenon be, the antagonism is quite obvious as shown by the failure of toxic blood levels of barbiturates to produce their expected effects in the presence of pentylenetetrazol.

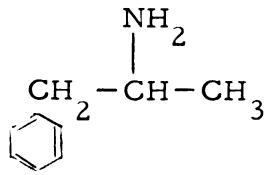
2. Induction of vomiting--Pentylenetetrazol in normal convulsive doses stimulates the vomiting center. Schwartz (1928) showed that pentylenetetrazol is capable of denarcotizing the emetic mechanism depressed by barbiturates. This denarcotizing effect further emphasizes their physiological antagonism. Pentylenetetrazol can induce vomiting as long as 7 hours after the administration in combination with barbiturates and so in such cases acts as a long acting drug. It was later shown by Fezekas and Koppanyi (1954) that large oral doses of Metrazol may act even up to 24 hours.

3. Delayed absorption--Van Liere and Northrup (1941) showed that sodium amytal caused an average decrease in emptying time of the stomach by about 20 percent, thus allowing quick passage of the barbiturate into the intestines to be absorbed, while pentylenetetrazol by counteracting this effect tends to slow down passage to the intestines. Whatever the reason, it is shown that the blood levels obtained by doses of barbiturates in combination with pentylenetetrazol are much lower than those obtained by the same doses of barbiturates alone. At the same time blood levels of barbiturates in the presence of pentylenetetrazol are much less effective than when alone. So it is a double restraint on barbiturates.

It is interesting to note that in spite of this antagonism, Metrazol does not interfere with the hypnotic effects of barbiturates (Koppanyi and Fezekas, 1953), and that the therapeutic combinations of barbiturates and Metrazol are very safe hypnotics.

AMPHETAMINE

Chemically--Racemic β phenyl isopropyl amine or α phenyl β amino propane.



It exists in three isomeric forms--levo, dextro, and dl beta or racemic form. The racemic form is commonly referred to as amphelamine, dextro form is called Dextroamphetamine and is the most potent, while levo form is the least potent in all the isomers.

Proprietary names--Benzedrine, Amfetsul etc.

Pharmacological actions--Amphetamine is a sympathomimetic like epinephrine but differs from it in quite a few properties viz. (1) It is resistant to enzymatic destruction in the gastrointestinal tract and so can be given orally. (2) It shows no synergism with cocain or reversal effect with ergotamine.

Amphetamine is a strong inhibitor of amine oxidase and according to Goddum and Kwaitkowski (1938), it would act by preventing the oxidation of epinephrine by amine oxidase and by competing with epinephrine for the receptor substance in the effector cells. However there are many unsolved problems which prevent the full acceptance of this theory and further investigation is needed to elucidate the mechanism of sympathomimetic action of amphetamine on CNS. Amphetamine is a

potent CNS stimulant. It stimulates cerebrospinal axis, especially the brain stem and the cortex. It is a potent agent for stimulating the medullary respiratory and other medullary centers, and lessening the degree of central depression caused by anesthetics, narcotics, hypnotics etc. Larger doses can cause excitation mainly due to stimulation. It does not produce seizures or subconvulsive dysrhythmias in normal animals. Indeed the drug can obtund the maximal electroshock seizure discharge and prolong the recovery period after such seizures, and these properties may be related to its usefulness in certain cases of epilepsy.

It has a marked analeptic action and is very useful in abolishing or shortening the duration or decreasing the intensity of anesthesia. In small doses it shows some psychic effects in man, e.g. wakefulness, alertness, increased initiative and elevation of mood, enhanced confidence, euphoria, elation, lessened sense of fatigue, increased vasomotor and speech activity and increased ability to concentrate. It is said to inhibit production of fatigue particularly in monotonous skilled tasks and somewhat to restore performance in fatigued individuals. The wakeful psychologic effects are related to some unknown control stimulation (Abraham Myerson, 1940).

After prolonged use or after large doses of the drug, fatigue and mental depression or other such adverse effects may occur. It also exerts a direct analgesic effect by its central action.

When combined with morphine it enhances and prolongs the analgesic action of morphine in man while it decreases the drowsiness, dizziness and weakness caused by morphine. Though it potentiates the analgesic action of morphine, it largely eliminates the analgesic action of nitrous oxide.

Amphetamine has no ability to increase the respiration of brain inhibited by anesthetics or to increase oxygen consumption of normal brain tissue. The stimulant action of amphetamine on normal or anesthetized brains is yet unexplained and it is doubtful whether its peripheral sympathomimetic action can be profitably correlated at present with its excitatory effects on the CNS.

Amphetamine facilitates monosynaptic and polysynaptic transmissions in the spinal cord and enhances decebrate rigidity. It improves reflex activity and recovery responses even in decebrate and decorticate animals. This effect may be due to an increase in internuncial activity which compensates for the loss of facilitation from centers destroyed.

Respiratory effects--The respiration is first depressed (mostly in amplitude) probably reflexly with the rise in the blood pressure. Then it soon comes to preinjection level and then is further stimulated markedly in rate and amplitude both to increase the ventilation rate considerably (Alles, 1933).

Detrick, Millikan, Modern and Thienes (1937) observed that with the first dose of benzedrine (0.25-4 mg/kg) in dogs and cats anesthetized with pentobarbital, there was a marked increase in rate and depth of respirations. Subsequent doses produced successively smaller increases and finally often a decrease in rate. The actual mechanism of respiratory stimulation was not determined. However from the facts that the anesthetized animals showed obvious symptoms of CNS stimulation it may be inferred that the action was central.

According to Goodman and Gilman it affects respiration by two sources:

1. Stimulation of medullary respiratory center--It increases both rate and depth of the respiration to increase the ventilation. The effect is not well marked in normal subjects but quite marked when respiratory center has been depressed chemically.

2. Dilating the bronchioles--The effect is not so marked. The effect is weaker but much more prolonged than with epinephrine (Alles and Prinzmetal, 1933).

Cardiovascular responses--Adequate doses usually cause a rise in both systolic and diastolic pressures and an increase in cardiac output and work. These effects are apparently accomplished by a direct myocardial action and by peripheral constriction of arterioles (Goodman and Gilman)..

In man the cardiac output, pulmonary circulation time, vital capacity, BMR and respiratory dynamics were not changed (Altschule and Iglauer, 1940; Goodman and Gilman).

Amphetamine sulphate does not have a pronounced effect on cardiac muscle as demonstrated by the electrocardiograph (Meyerson, 1940). In several instances a transitory reflex slowing of pulse occurred in man at the onset of rise of arterial pressure. In some such cases a transitory slight increase in cardiac output was also detected (Altschule and Iglauer, 1940). Rise in B. P. in man is marked and lasts for 1-2 hours. The effect tends to lessen and disappear after the drug is used over an extended period (Meyerson, 1940). Benzedrine in ordinary clinical doses of 5-10 mgm in man has no significant effect on the cardiovascular dynamics (Altschule and Iglauer, 1940). Various arrhythmias, palpitation and precardial pains may occasionally be observed with this drug in normal as well as diseased persons. In normal man it has often been said to decrease cerebral blood flow and cerebral oxygen utilization accompanied with the rise in mean blood pressure.

Amphetamine causes vasoconstriction by stimulating the medullary vasoconstrictor center and the sympathetic receptive substance in the muscle cells of the blood vessels. On local application also it causes vasoconstriction in mucous membranes.

Detrick, Millikan, Modern and Thienes (1937) observed that the effect of benzedrine on blood pressure in dogs was very

irregular and varied over a wide range from decrease to an increase in normal B. P. ⅓ They also observed that ergotamine tartrate when used before could increase, decrease and even abolish the effects of the following amphetamine, and that cocaine decreased the pressor effect of amphetamine.

Addiction to amphetamine--The drug is neither habit forming nor have any untoward symptoms yet been observed by its constant use (Meyerson, 1940). While Connel (1958) states that addiction causes "delusions of persecutions and auditory and visual halucination indistinguishable from those occurring in paranoid schizophrenia."

Prolonged use of amphetamine in orthostatic hypotension to maintain B. P. in normal limits causes insomnia which is difficult to overcome by even full doses of barbiturates and lasts for 24-72 hours (Korns and Randall, 1938).

Fate and excretion--Beyer and Skinner (1940) in their experiments concluded that somewhat less than 50 percent of amphetamine was excreted in 48 hours following ingestion. In man the percentage excreted of a given dose generally paralleled the volume output of urine. The percentage excreted usually was greater for the smaller doses. In an attempt to account for the remainder of the drug dose several experiments were conducted to show that: (1) probably all the drug dose is absorbed from the gastrointestinal tract. (2) Hydrolysis of urine does not result in greater yield of amine. (3) Amine oxidase does not activate oxidative deamination of amphetamine.

The drug is apparently slowly and partially inactivated in the body by a loose combination with some agent normally contained therein. Whether the drug is then partially destroyed or excreted slowly over a period of several days, either free or so loosely combined as though not apparently conjugated is yet a problem.

Goodman and Gilman are of the opinion that 50 percent of amphetamine is destroyed in the body, principally by deamination in the liver, and 50 percent passes in urine unchanged. It quite resists deamination by amine oxidase by inhibiting it, and so its destruction is slow and its duration of action long. Other enzymes e.g. phenol oxidase etc. destroy it.

Barbiturate amphetamine antagonism--Alles (1933) observed that amphetamine intravenously "excited a considerable effect in waking the animal from barbital anesthesia." In man, Meyerson et al. (1936) reported that Benzedrine sulphate subcutaneously did not affect the depth, although it definitely shortened the duration of soluble amytal narcosis, and they stated that hypertension produced by Benzedrine sulphate subcutaneously could be reduced by soluble amytal intravenously and also that hypotension produced by soluble amytal intravenously could be elevated by Benzedrine sulphate subcutaneously. They also observed that Benzedrine sulphate considerably stimulates the respiration depressed by barbiturates. A valuable evidence of antagonistic action of Benzedrine sulphate to soluble amytal in man was produced by

Reifenstein and Davidoff (1938) when they brought their ten volunteers out of deep narcosis produced by 7 1/2 grains of soluble amytal intravenously in each, by 1, 2 or 3 intravenous injections of 10 mg of Benzedrine sulphate, within an hour of narcosis.

Freireich and Landsberg (1946) treated 14 barbiturate poisoned patients with intravenous injections of amphetamine. Thirteen patients recovered without any observable ill effects except for some headache. The patient who died could not be given a full dose because no more of the drug was available.

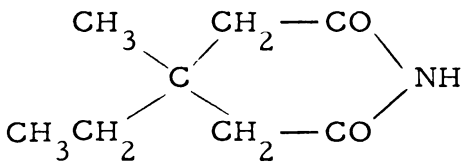
Lee and Alfredson (1952) observed that the threshold of the respiratory response to sciatic stimulation raised enormously by deep pentobarbital depression was decreased almost to its previous level by amphetamine, thereby indicating that both these drugs acted on the central respiratory mechanism. They also found that a dose level of 2.5 mg of amphetamine per kilogram body weight would be sufficient to combat the depressant effect of large doses of pentobarbital on the blood pressure in dogs.

Linked with this relationship of amphetamine sulphate to the barbiturates is what is elsewhere called their "reciprocal pharmacology." If one desires to obtain a sedative effect with the barbiturates and seeks to avoid the hangover and the depression which these drugs tend to produce, the addition of small doses of amphetamine sulphate is of value.

Amphetamine has a wide margin of safety while picrotoxin has a narrow one. (It may easily cause convulsions while the patient continues to be in coma too.) To eliminate this, a sometimes serious effect of picrotoxin, Billow (1950) used Benzedrine sulphate conjointly with picrotoxin which proved to be highly efficacious. He also pointed that such a combination not only helps in barbiturate intoxication, but also from resultant circulatory collapse, myocardial ischemia, hypoxia, necrosis, infarction and pulmonary complications. Billow in his experiment used picrotoxin intravenously and Benzedrine sulphate intramuscularly.

METHETHARIMIDE

Chemically--3. 3 methyl ethyl glutarimide or ββ methyl ethyl glutarimide.



Proprietary names--Mikedimide (solution in propylene glycol) Bemegride, Megimide (solution in water).

Pharmacological actions--3. 3 methyl ethyl glutarimide is a CNS stimulant and in high dosage and particularly if given rapidly will cause convulsions in both barbiturized and normal animals (Benica and Wilson, 1950; Shaw et al., 1954). However full animal investigation (Shaw and Bentley, 1952; Shaw et al., 1954) has indicated that this substance possesses a high therapeutic index. In therapeutic doses it is a useful analeptic against barbiturate depression.

3. 3 methyl ethyl glutarimide in therapeutic doses appears to cause a slight rise in blood pressure, and a large dose given intravenously to a barbiturized patient has produced a large rise in blood pressure and sweating suggesting a direct effect on the autonomic ganglia (Shulman et al., 1955).

Excretion--Much of the 3 3 methyl ethyl glutarimide is excreted in the urine unchanged (Schulman et al., 1955).

Mikedimide barbiturate antagonism--3. 3 methyl ethyl glutarimide appears to possess a specific respiratory stimulation effect only in the barbitalised animals and routinely it suggests valuable use to terminate barbiturate anesthesia, shorten the sleeping time, restore reflex activity and minimize the need for prolonged medical attention. The drug appears to be a specific barbiturate antagonist on almost a milligram for milligram basis (Baker and Englewood, 1956).

Boyan et al. (1958) found by servocontrolled cross over experiments that Megimide is 1. 73 times as potent as Metrazol in reversing the electroencephalographic effects of thiopental in man.

Oriordan and Breward (1958) compared Megimide with picrotoxin, nikethamide and a combination of Megimide and deplazole for their analeptic properties on 55 patients anesthetized with thiopentane for minor surgery and found best results with Megimide, and its combination with deplazole. They said, "Whatever the exact pharmacological action of Megimide will prove to be, its specificity for the barbiturate series is marked." In support of this specificity they further found that Megimide is not effective against other anesthetics e. g. cyclopropane, trichlor ethylene, ethyl ether etc.

Mechanism of antagonism--Shulman et al. (1955) observed that "if after the patient has been brought to the 'safe state' his condition regresses, further small treatments may be given as required. Regression is more likely to occur when the coma has lasted a long time before

treatment is started, or if the barbiturate concerned is a long acting one (e. g. phenobarbitone)." This makes one to conclude that Megimide does not directly chemically antagonize the barbiturates as then this regression would not occur.

3. 3 methyl ethyl glutarimide due to its structural similarity to barbiturates "has been postulated to be either a barbiturate inactivator or a competitor for the same substrate in the brain" (Boyan et al., 1957).

This view has been partly contradicted by Kimura and Richards (1958) who hold the opinion that Megimide is not a competitive antagonist to barbiturates but merely another drug which stimulates the CNS as do picrotoxin and Metrazol.

The work of Boyan et al. (1957) attempts to indicate a new explanation for this antagonism.

A patient who had been in deep barbiturate narcosis for 57 hours was given 5500 mgms Megimide. This resulted in clinical improvement and there were no signs of overdosage of this drug. The electroencephalographic pattern changed from a deeper to a lighter level of anesthesia, and when the electroencephalogram stopped improving despite continued treatment with Megimide, it was decided that the maximum therapeutic effect of the drug had been reached at that time and its administration was discontinued. The drug corrected the circulatory and respiratory depressions successfully.

A transient increase of oxybarbiturate level of plasma was found after Megimide administration though the electroencephalographic

level was improving towards a lighter level of anesthesia. This was explained by Butler and Walell who showed that undissociated barbiturate is absorbed into the brain while dissociate barbiturate remains largely in the plasma. An equilibrium is established between the plasma and the brain barbiturate concentrations. Increasing the plasma pH increases dissociation of barbiturate and shifts this equilibrium so that ultimately the plasma barbiturate level increases and brain barbiturate level decreases. This may also explain why the patient was more responsive even though the oxybarbiturate level of the blood had increased.

Plum and Swanson (1957) in their experiments concluded the following, most of which go against the drug:

> ββmethyl ethyl glutarimide showed little evidence of true barbiturate antagonism but appeared to possess nonspecific analeptic properties. The analeptic effects were more rapid in onset than those of picrotoxin and there were fewer undesirable side reactions.
>
> ββmethyl ethyl glutarimide however failed to stimulate spontaneous breathing in an animal receiving more than 1.4 times the lethal dose in untreated animals. The pressor response of the drug was more reliable in lightly anesthetized animals than in deeply comatose animals. Its properties of CNS stimulation appeared similar to but less intense than those of picrotoxin.
>
> There was little convincing evidence that 3.3 methyl ethyl glutarimide shortened coma although muscle spasms were produced with ease as was accentuation of stretch reflexes.

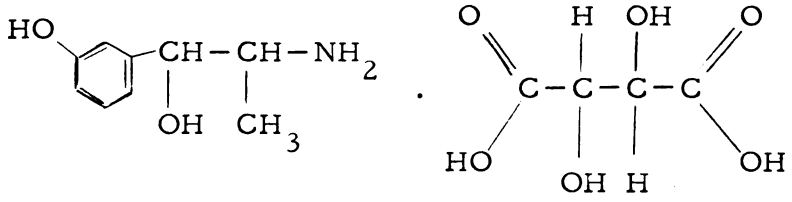
J. Pederson has observed that the drug does not shorten coma or hasten the rate of elimination of barbiturates from the blood. "The experimental and clinical data" from the laboratory as observed

by Plum and Swanson (1957) "thus indicate that responsiveness to $\beta\beta$ methyl ethyl glutarimide as a stimulant is inversely related to the depth of narcosis."

The author has not attempted to make any distinction between Megimide and Mikedimide in the review as both are essentially the same chemically but there might be some difference between the two because of their solvents and concentrations. Megimide is a 0.5 percent solution in water and Mikedimide is a 3 percent in propylene glycol of 3.3 methyl ethyl glutarimide. Propylene glycol is excreted unchanged via the urine as the 3.3 methyl ethyl glutarimide is understood to be. Kidneys can also actively concentrate propylene glycol. Propylene glycol is also a CNS depressant in large doses, but it seems to be devoid of any demonstrable toxicity when administered in smaller though still larger total doses for prolonged periods. So it is hard to say what effect, if any, propylene glycol will have on the effects of 3.3 methyl ethyl glutarimide, in such small doses as administered with 3.3 methyl ethyl glutarimide as Mikedimide.

METARAMINOL-BITARTRATE

Chemically-- -1(m-hydroxyphenyl) 2-amino 1-propanol d-hydrogen tartrate or α(1 amino·ethyl) m hydroxybenzyl alcohol hydrogen d tartrate.



Proprietary name--Aramine.

Pharmacological actions--Metaraminol bitartrate is a sympathomimetic amine. Studies on it have by now mostly remained centered around its cardiovascular effects, and not much can be said very definitely about its other effects.

On the CNS it is said to produce less stimulation than ephedrine (N. N. R., 1959). In hypotension it increases cerebral blood flow and relieves hypoxia and so tends to improve the state of consciousness (Mayer et al., 1955)

On blood pressure--Metaraminol bitartrate is a potent vasopressor with prolonged duration of action. It elevates both systolic and diastolic pressure and due to increased blood pressure, the cerebral, renal and coronary blood flow also improve (N. N. R., 1959). Pulse pressure appears to be increased moderately, and it does not produce a primary or secondary fall in blood pressure under experimental conditions studied so far (Poe, 1954).

The pharmacologic activity of metaraminol bitartrate is primarily vasopressor and does not include the anorexigenic or cardio-accelerator effects (Weil, 1957).

Mayer et al. (1955) showed that in hypotension metaraminol bitartrate increases cerebral blood flow and relieves hypoxia if any. But on the other hand, in normal dogs Aramine decreases cerebral blood flow by causing hypertension.

The drug thus is of value against hypotension, but treatment of patients with chronic orthostatic hypotension of ideopathic type and postural hypotension related to neurologic disturbances was less successful (Weil, 1957). The Council on Drugs in 1957 reported that because of a more gradual onset and prolonged duration of action maintenance of blood pressure with metaraminol bitartrate is generally more smooth and is subject to fewer of the abrupt variations and excessive responses sometimes observed with other pressor agents. It is non-irritant to tissues and is effective by oral as well as parenteral routes. Taylor (1952) observed on local applications of Aramine (metaraminol bitartrate) to nasal mucosa that it does not cause secondary vasodilation, and its vasoconstrictor action is prolonged but not sufficient to cause endothelial anoxia.

On the heart--Unlike most pressor amines, Aramine slows the heart rate. This effect appears to be predominately a reflex response to the increase in blood pressure (Poe, 1954). It is said to have no toxic

effect on the heart.

On the other hand New and Nonofficial Drugs (1959) mentions that "Aramine exerts a moderately positive inotropic effect on heart and does not appear to provoke cardiac arrhythmias in the sensitized myocardium."

Weil (1955) states that metaraminol bitartrate is without specific effects on cardiac output and that it increases coronary blood flow. In normal man Aramine does not significantly effect the cardiac output (Livesay et al., 1954). In vagotomized animals it increased cardiac output while right and left atrial pressures fell down. Larger doses of Aramine had little further effect on cardiac output though increased the blood pressure by its vasopressor effect (Mayer and Beazley, 1955 and Sarnoff et al., 1954).

Bradycardia, prominent in normotensive volunteers, was uncommon in hypotensive patients when treated with Aramine (Weil, 1955). Sarnoff et al. (1954) showed that Aramine tends to decrease the elevated atrial pressure to normal but tendency to decrease it below normal is very little. Effect is more marked on the left atrium. A dose of 0.03 mg/kg markedly increased the myocardial contractibility but additional doses did not greatly enhance it. That this increased cardiac contractility is not simply due to increased coronary blood flow, is indicated by the fact that 2 minutes prior to the injection of Aramine, mechanical coronary perfusion at the rate of 257 cc per minute for 1 1/2

minutes had failed to produce a similar salutary effect. It is of additional interest that the myocardium did not require a greater blood flow per unit of work performed after the administration of this agent, nor did it produce significant arrhythmias in the presence of severe myocardial hypoxia.

Mechanism of action--Metaraminol bitartrate contracts the peripheral vascular bed, increases venous return and coronary blood flow and acts directly on the heart muscle to increase its contractility (Weil, 1955).

Aramine tends to increase the blood pressure in hypotensive, normotensive as well as hypertensive animals by its pressor and cardiac effects but in normotensive animals the blood pressure rise to hypertensive levels is opposed by the reflex vagus stimulation. Atropine can block this vagal effect without affecting the pressor effect. In vagotomized animals the blood pressure does go to the anticipated hypertensive levels and there is no bradycardia or any blood vascular reflex effect (Sarnoff et al., 1954).

Metaraminol bitartrate is long acting presumably because of structural insusceptibility to the actions of phenol and amine oxidases (Weil, 1955).

On the respiratory system--In normotensive volunteers metaraminol bitartrate caused "subjective shortness of breath" and "tachypnea." Livesay et al. (1954) observed no consistent effect on respiration in the normal volunteers. However several individuals showed increased

respiratory rate as blood pressure was elevated. Several of them complained of a sense of constriction in the chest without pain. Pulmonary artery pressure increased markedly with Aramine. Arteriovenous oxygen difference increased from 4. 5 vol percent to 5 vol percent and oxygen consumption also went up.

On the kidney--Renal function is improved in hypotensive (by bleeding) dogs by metaraminol bitartrate as the blood pressure improves and so improves the renal blood flow and the glomerular filtration rate (Moyer et al., 1954). In normal man the renal function is decreased by metaraminol bitartrate as it causes constriction of renal blood vessels and so decreases renal blood flow and glomerular filtration rate (Livesay et al., 1954).

CHAPTER II

MATERIALS AND METHODS

Experimental animals and drugs--The dogs used in all the experiments were obtained from a city dog pound. These animals had been kept in individual cages and maintained on a commercial food diet and water ad libitum. Efforts were made to use dogs weighing about 9 to 13 kilograms, but due to the large number of dogs required, sometimes heavier and lighter dogs had also to be used. Care was taken not to use any dog operated or anesthetized or used for any other experiment in at least the preceding 7 days, and usually the unused dogs were selected. No consideration for any breed was taken.

The pentobarbital sodium employed was in a 3 percent solution in 10 percent ethyl alcohol freshly prepared before use.

Picrotoxin was a 0.3 percent solution (Abbott Laboratories).

Pentylenetetrazol was a 10 percent aqueous solution (Metrazol, Knoll Pharmaceutical Company).

Amphetamine sulfate (racemic) was a 5 percent aqueous solution (Haver Glover Laboratories).

Methetharimide was a 3 percent solution in propylene glycol (Mikedimide, Parlam Corporation).

Metaraminol bitartrate used was a 1 percent aqueous solution (Aramine, Merck, Sharp and Dohme).

Experimental procedure--At the beginning of the experiment the dog was weighed and then carefully given pentobarbital sodium intravenously over about 10 minutes until the dog was in deep anesthesia, and the respiratory rate had slowed down markedly. A rubber tracheal tube with an inflation cuff around its distal end was then passed into the trachea through the mouth, and the cuff was inflated. Degree of inflation was indicated by a pilot balloon. This made the tracheal tube to fit snugly into the trachea and air could pass freely into the trachea and out, only through the tracheal tube.

The dog was connected by the tracheal tube to the apparatus to record the respiratory volume and the respiratory rate.

The values for respiratory volume were obtained by measuring the expired air by means of a wet test gas meter connected through the necessary valve system to the tracheal tube. The gas meter was modified in the laboratory here in such a fashion as to record each 250 cc by means of an electrically operated signal magnet. A small tube from the air valves was attached to a tambour which had one electrode attached to its diaphragm and the other just above it so that with each expiration and inspiration there was an inflation and collapse and so a make and break of the circuit to another electrical signal magnet. A third signal magnet was used as a timer for every 5 seconds. Ink writing points were attached to all signal magnets to write on a white kymograph paper belt.

The minute respiratory volume was now observed for a few minutes and if it was near about 1. 5 liters per minute the dog was set for trying the analeptic combination. If the minute respiratory volume was higher than more of pentobarbital was slowly injected intravenously to lower it to about 1. 5 liters per minute. Sometimes some dogs, particularly with the shallow panting respirations, showed an abrupt fall in the respiratory minute volume after showing some sort of resistance to the anesthetic to a certain level.

After bringing the respiratory minute volume of the dog to about 1. 5 liters or lower the analeptic combination was administered intravenously and the effect observed for 40 minutes to 1 hour. To prepare the analeptic combination half the indicated therapeutic doses of 2 analeptics were either mixed in the syringe or given one after the other by the same needle intravenously. Mikedimide, due to its solvent propylene glycol could not be mixed with aqueous solutions of other analeptics and so was always given just preceding the other analeptic, both through the same needle. In this way all the possible 10 combinations from the 5 analeptics mentioned were tried. Each combination was tried on at least 6 dogs usually.

All drugs were injected intravenously either by cephalic or saphenous vein. Quite frequently while manipulating and pricking the barbitallized animal for injection of the analeptic, it was observed that the ventilation increased a little bit even before the analeptic was injected. This effect evidently is reflexly due to the mechanical stimulation at the site of injection.

CHAPTER III

RESULTS

The effect of these combinations and individual drugs tested on ventilation is found to be in the following descending order of efficiency:

Methetharimide - Amphetamine

Amphetamine - Metaraminol bitartrate

Amphetamine - Pentylenetetrazol

Methetharimide - Picrotoxin

Amphetamine - Picrotoxin

Metaraminol bitartrate

Methetharimide - Metaraminol bitartrate

Methetharimide - Pentylenetetrazol

Metaraminol bitartrate - Picrotoxin

Metaraminol bitartrate - Pentylenetetrazol

Pentylenetetrazol - Picrotoxin

Combinations of methetharimide besides had distinct awakening effects on the barbitallized dogs as evidenced by quite frequent return of paw, corneal and palpebral and even sometimes cough reflexes, and many times the dogs showed paddling movements and coughing as soon as the tracheal tube was taken out of them for detaching them from the apparatus at the end of the experiment. This shows the superior awakening property of methetharimide.

At the same time these dogs receiving the combinations of methetharimide showed peculiar trembling and body bending movements during each inspiration, relaxing on expiration as if the dog had to strain a lot for inspiring air and could expire quite easily. This phenomenon was observed quite frequently and sooner or later after the analeptic injection. These movements continued even when the dogs were removed from the apparatus after the experiment and till they recovered their normal senses, when they started respiring quite normally.

Amphetamine appears to be the best choice among these analeptics for a combination with most of the drugs. It seems to improve and maintain the ventilation at at least quite a respectable level for a considerable period. The next in order are methetharimide which is again quite superior over metaraminol bitartrate, picrotoxin and pentylenetetrazol. Pentylenetetrazol appears to be quite poor for a combination and seems to drag down even the normally expected effect of the other drug somehow.

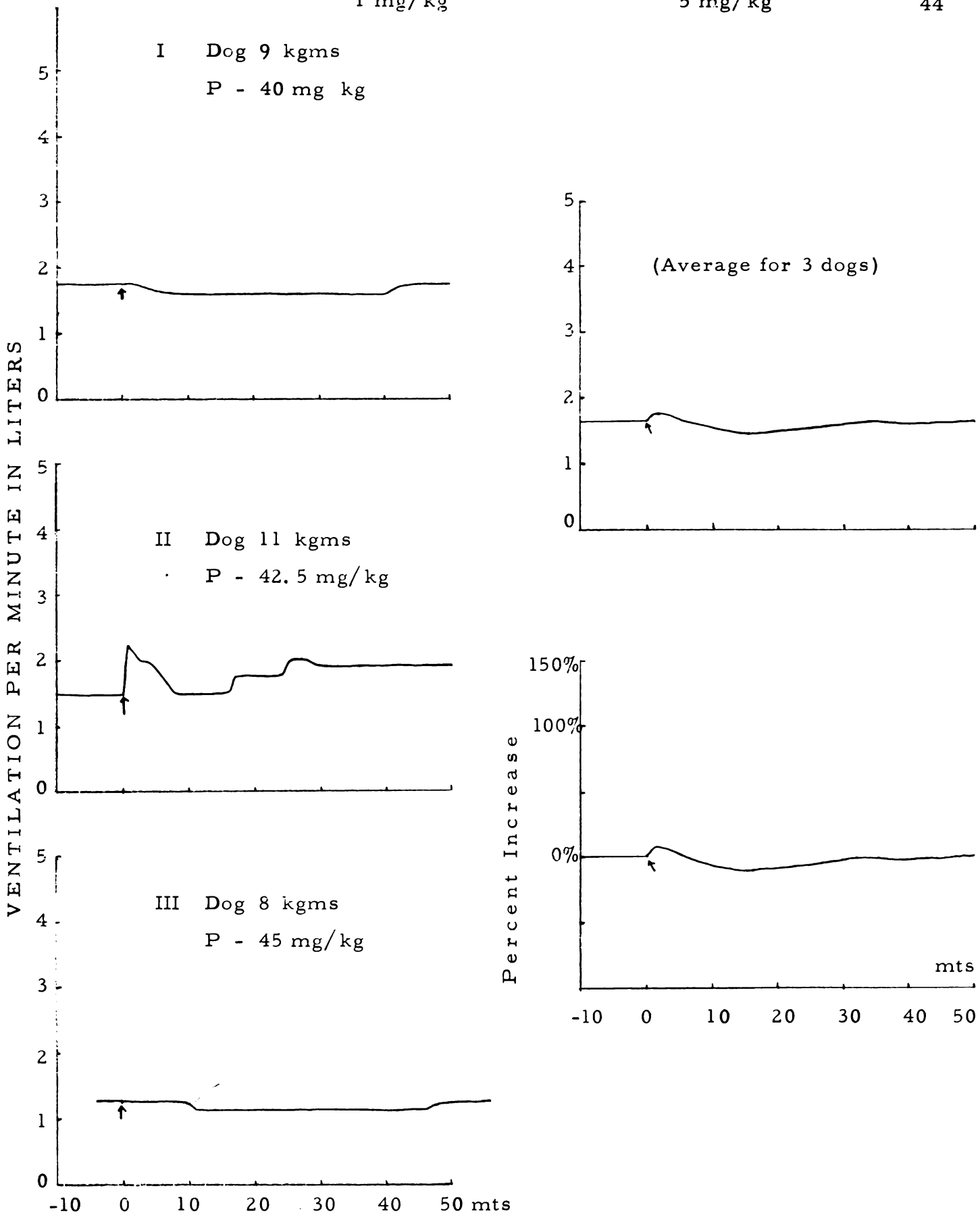
Abbreviations in the Graphs

Me	Methetharimide	Pi	Picrotoxin
A	Amphetamine	Pe	Pentylenetetrazol
MB	Metaraminol bitartrate	P	Pentobarbital

In case both the drugs of the analeptic combinations were mixed in the same syringe and injected at one time the injection is shown by a single arrow with no sign on it, otherwise arrows indicating other injections bear the abbreviations for the drug injected.

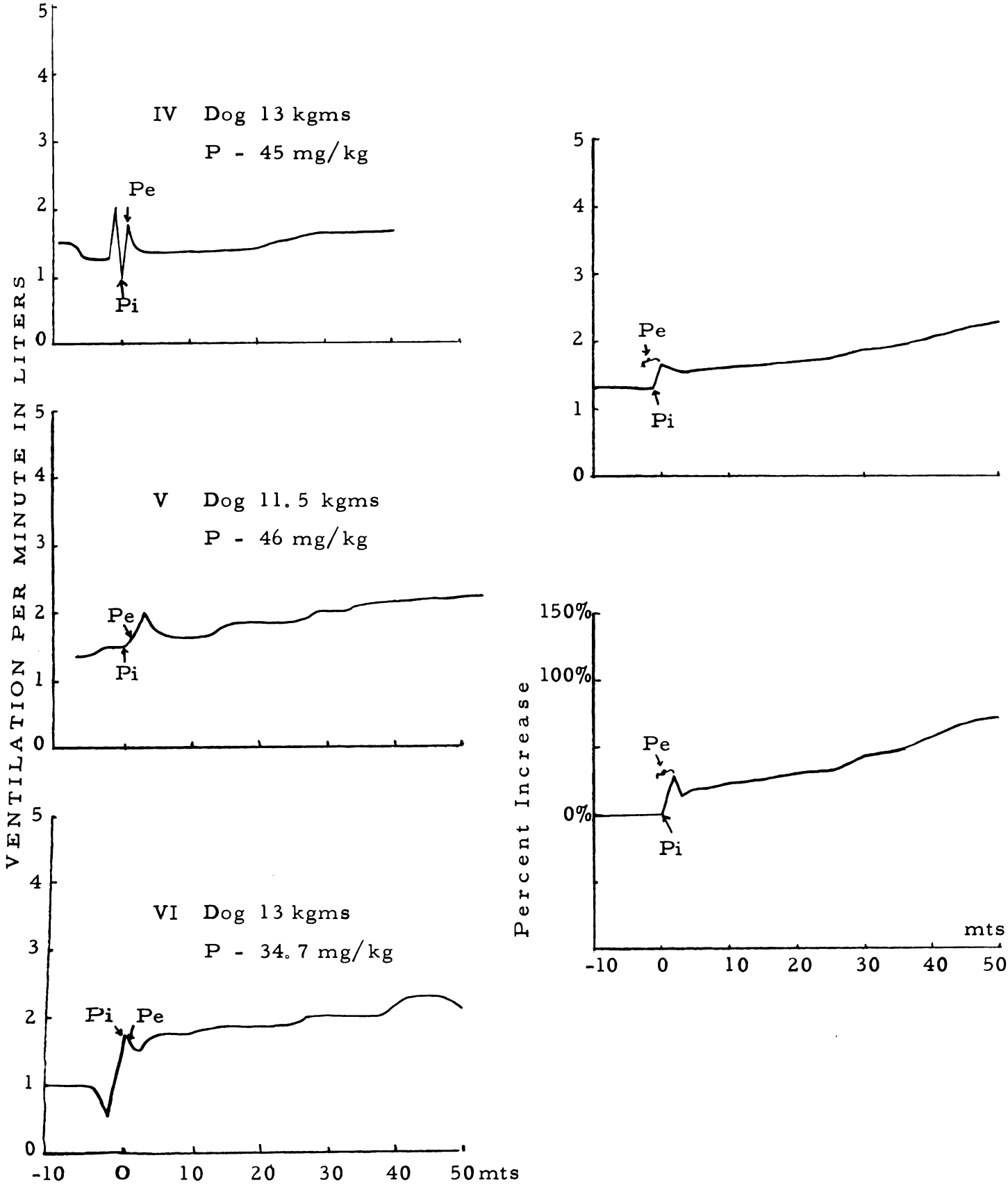
PICROTOXIN – PENTYLENETETRAZOL

1 mg/kg 5 mg/kg

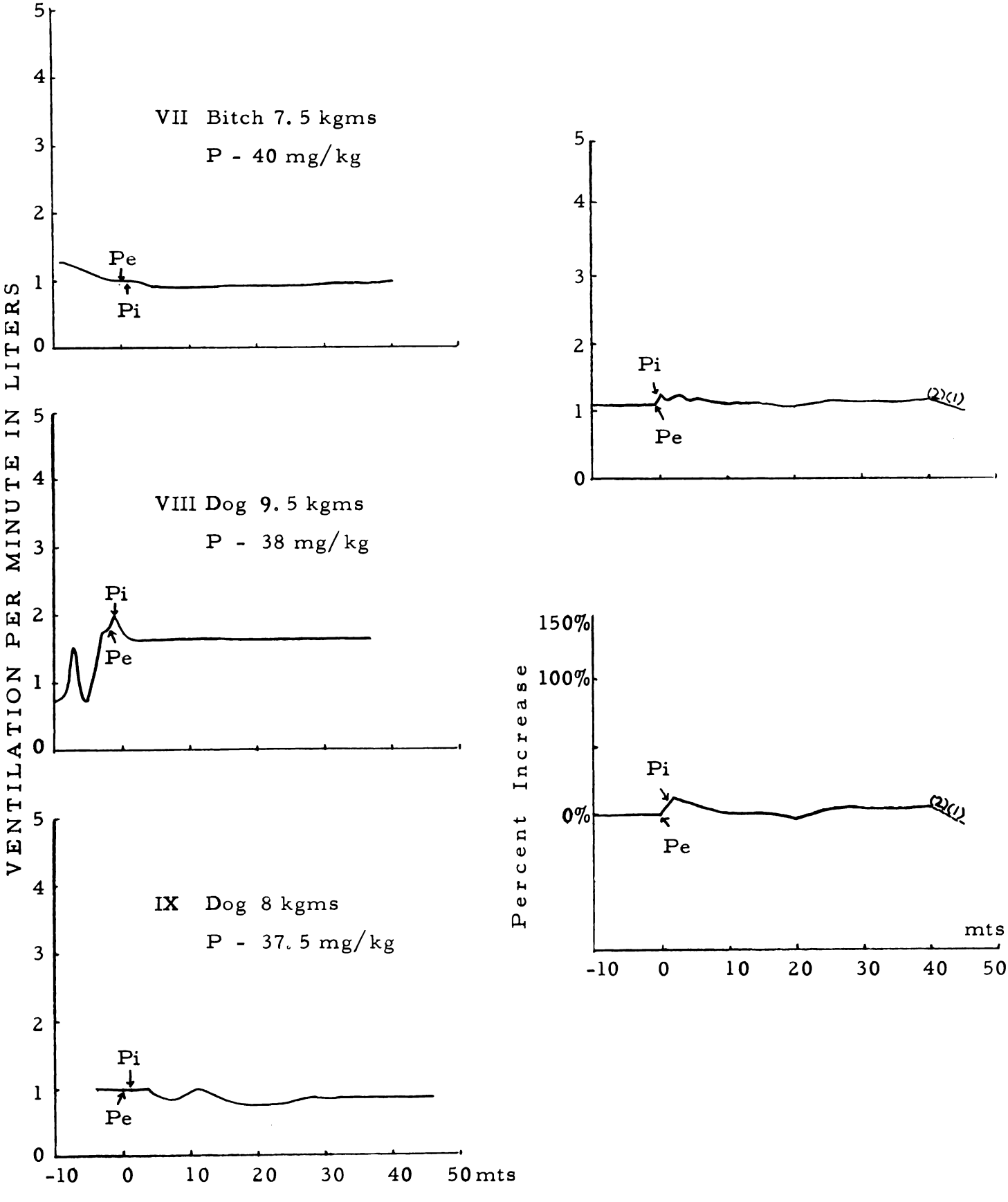


PICROTOXIN → PENTYLENETETRAZOL

1 mg/kg 5 mg/kg

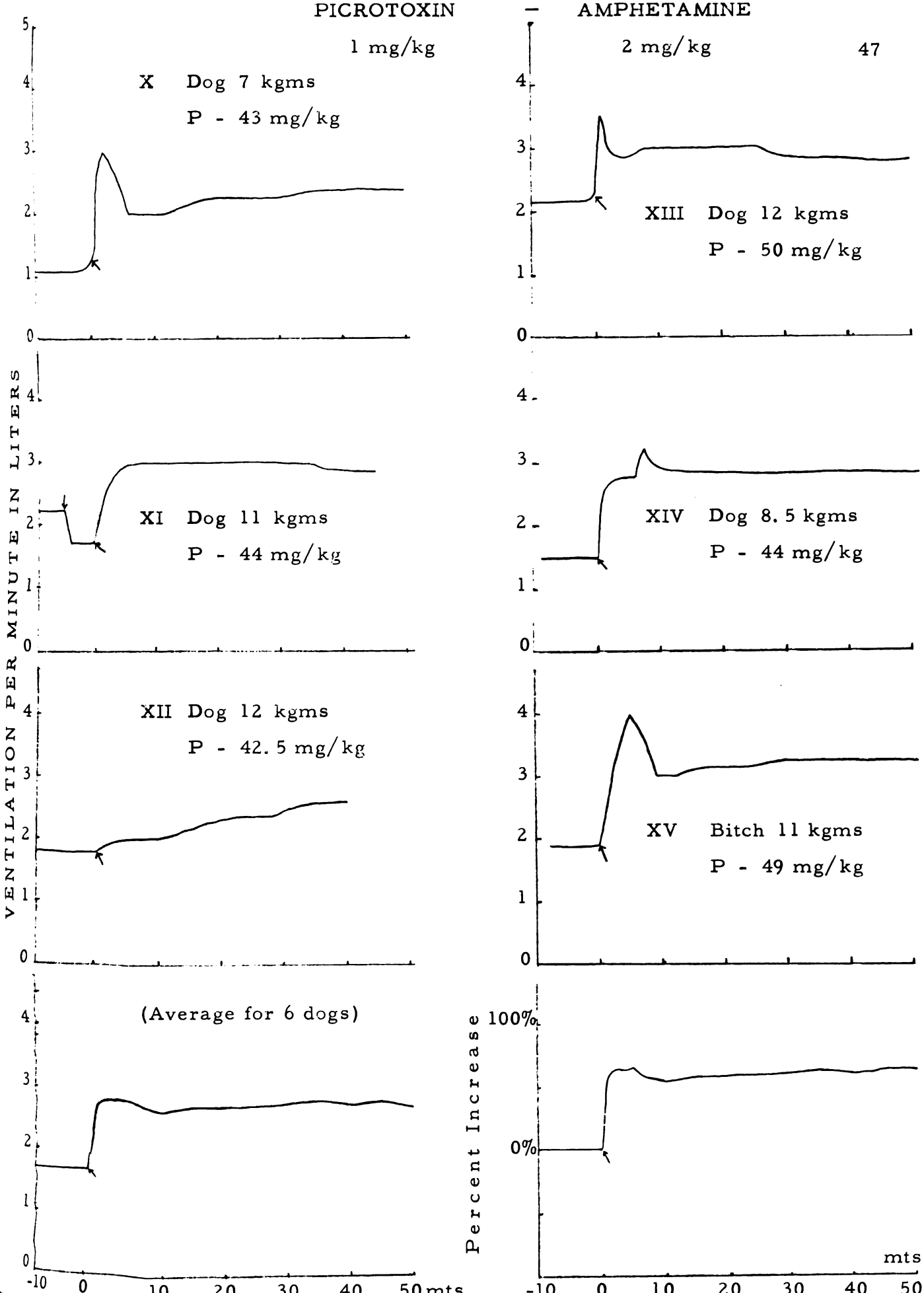


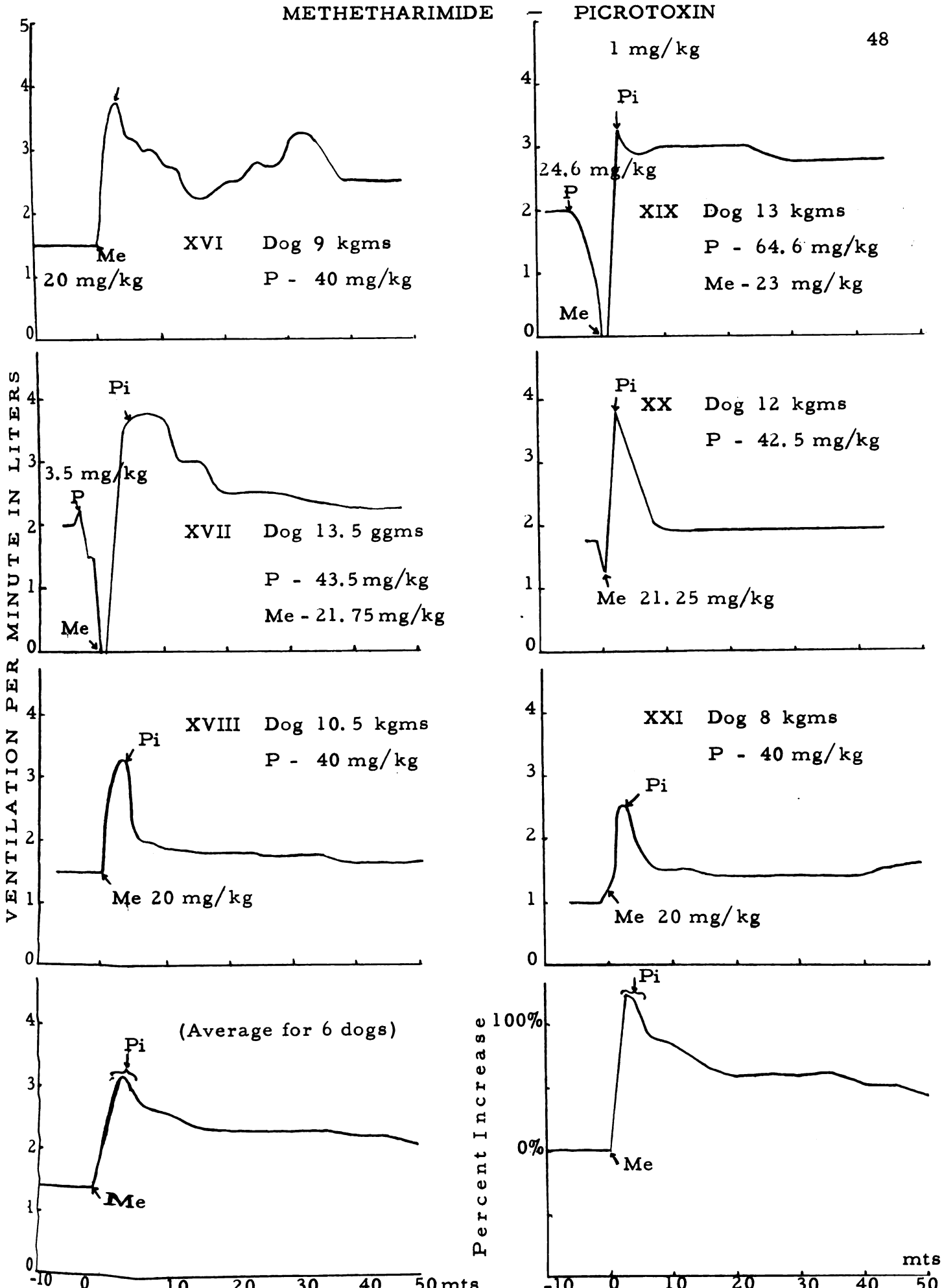
PENTYLENETETRAZOL 5 mg/kg → PICROTOXIN 1 mg/kg

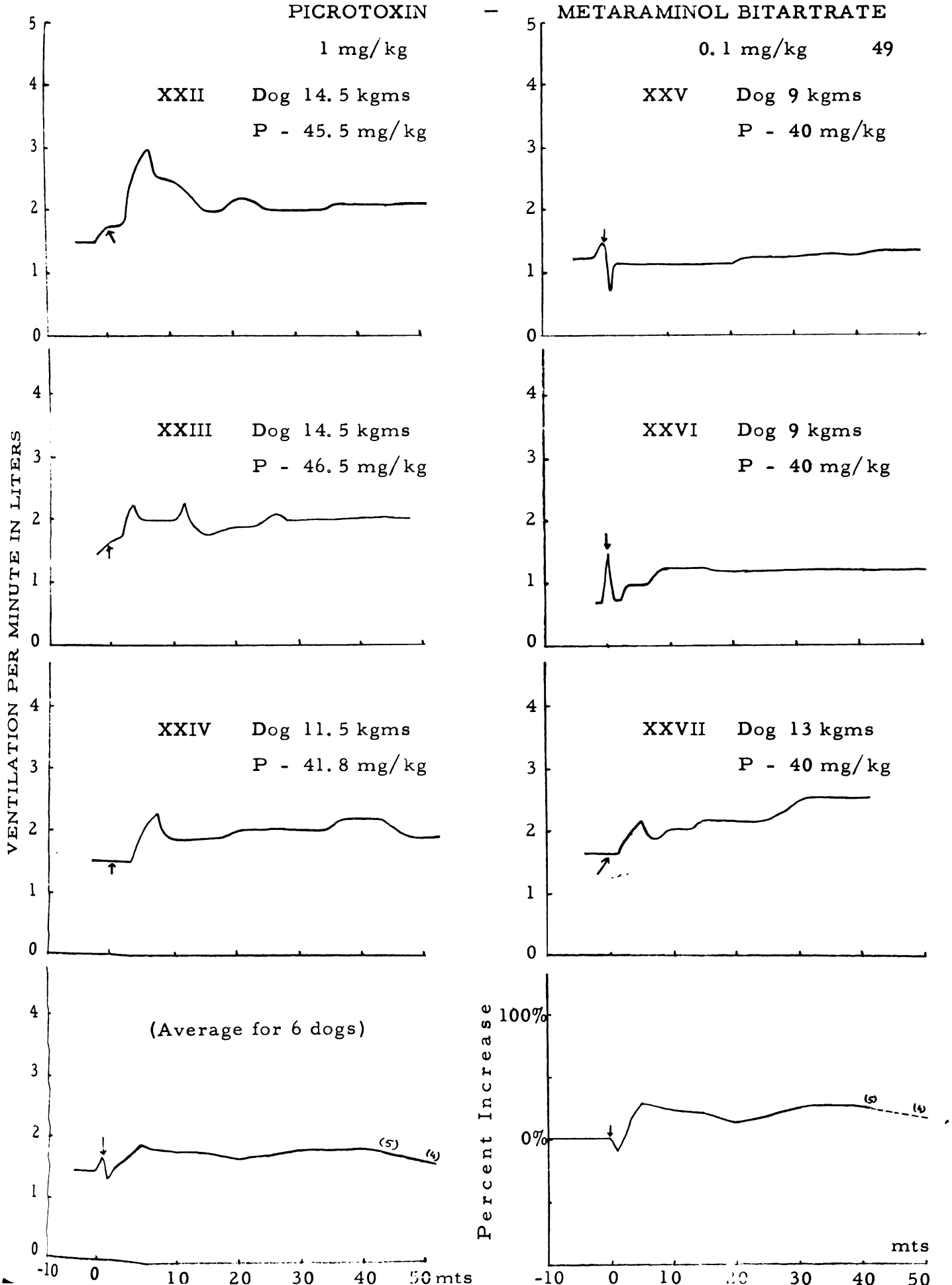


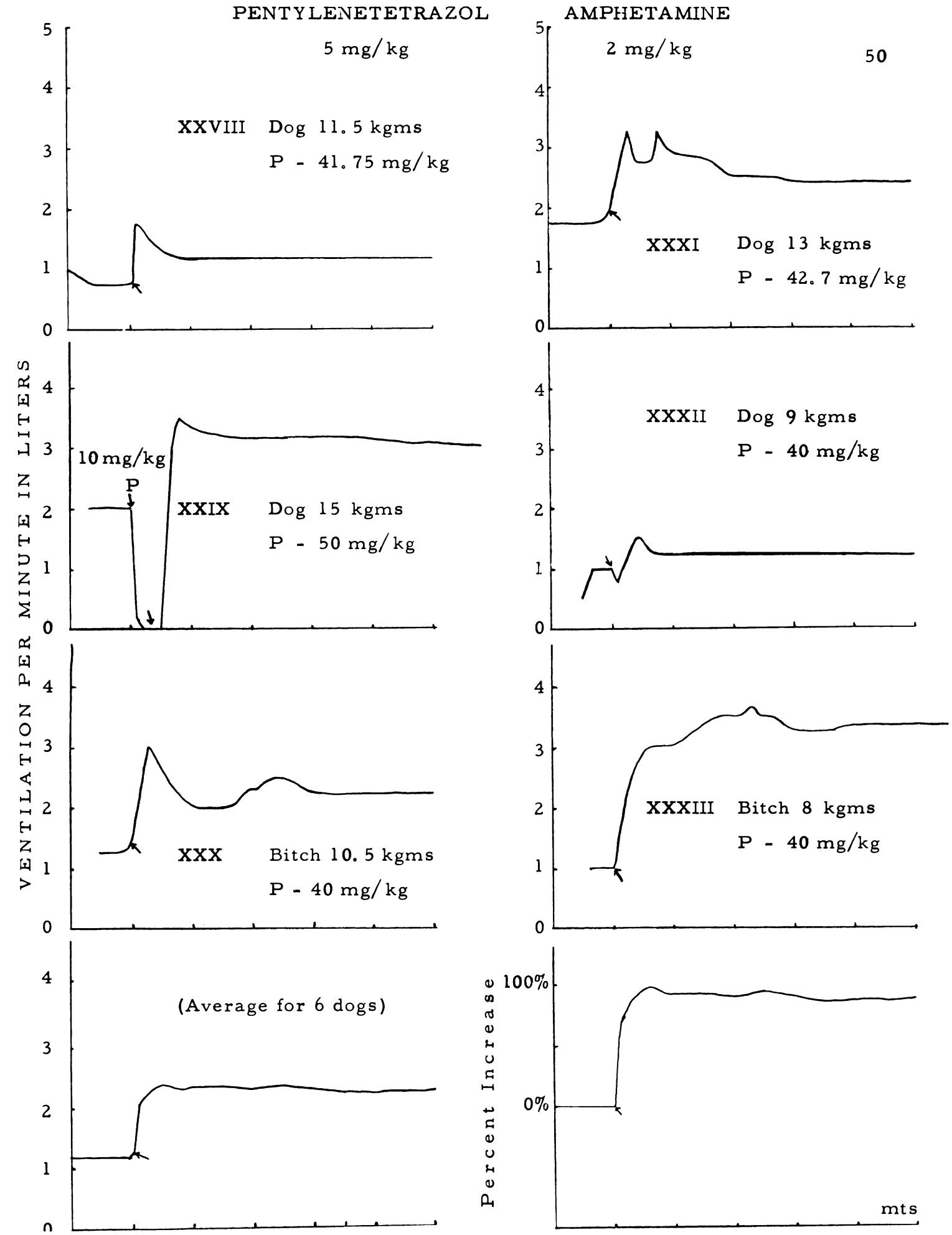
PICROTOXIN — AMPHETAMINE

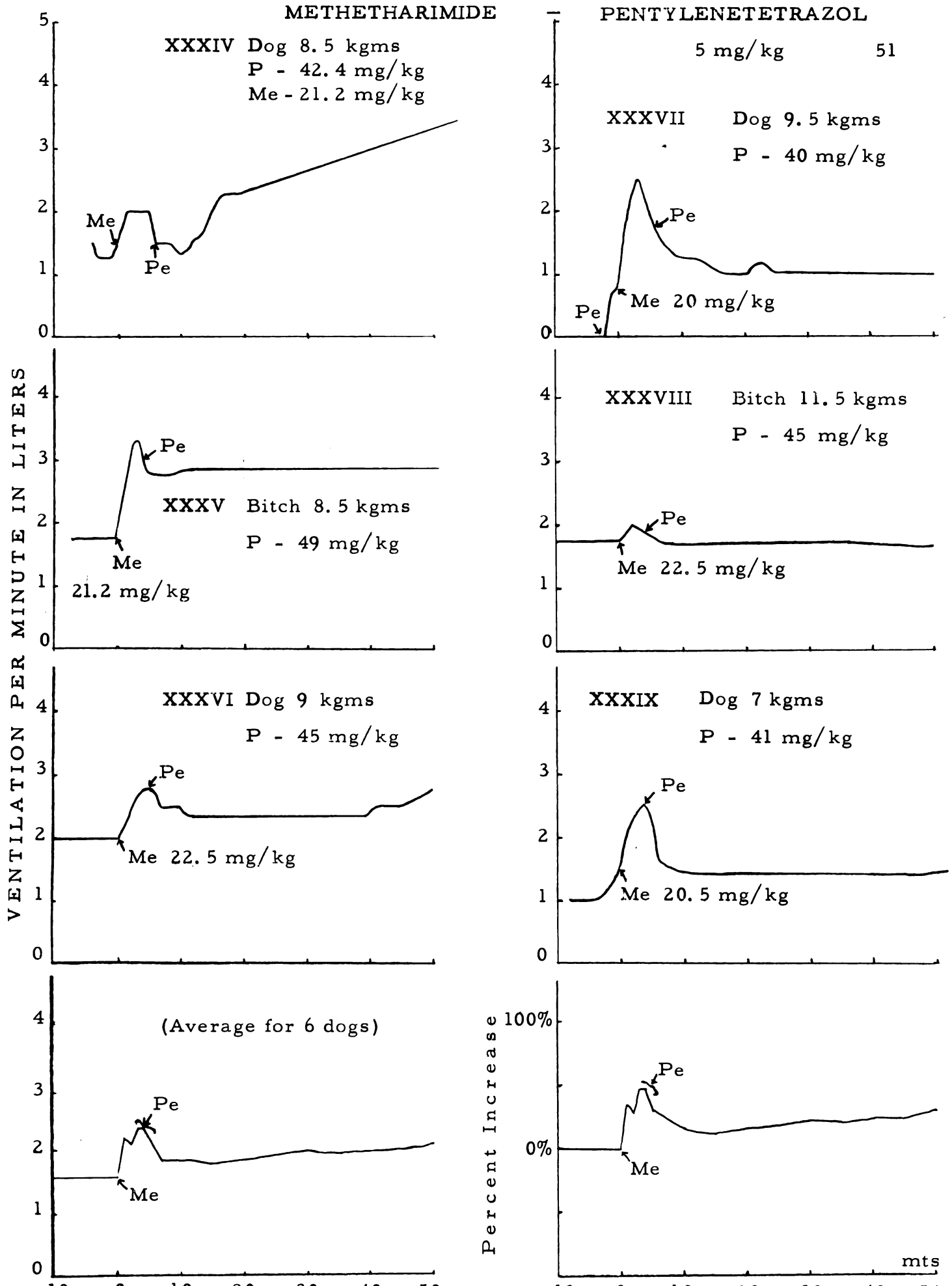
1 mg/kg — 2 mg/kg



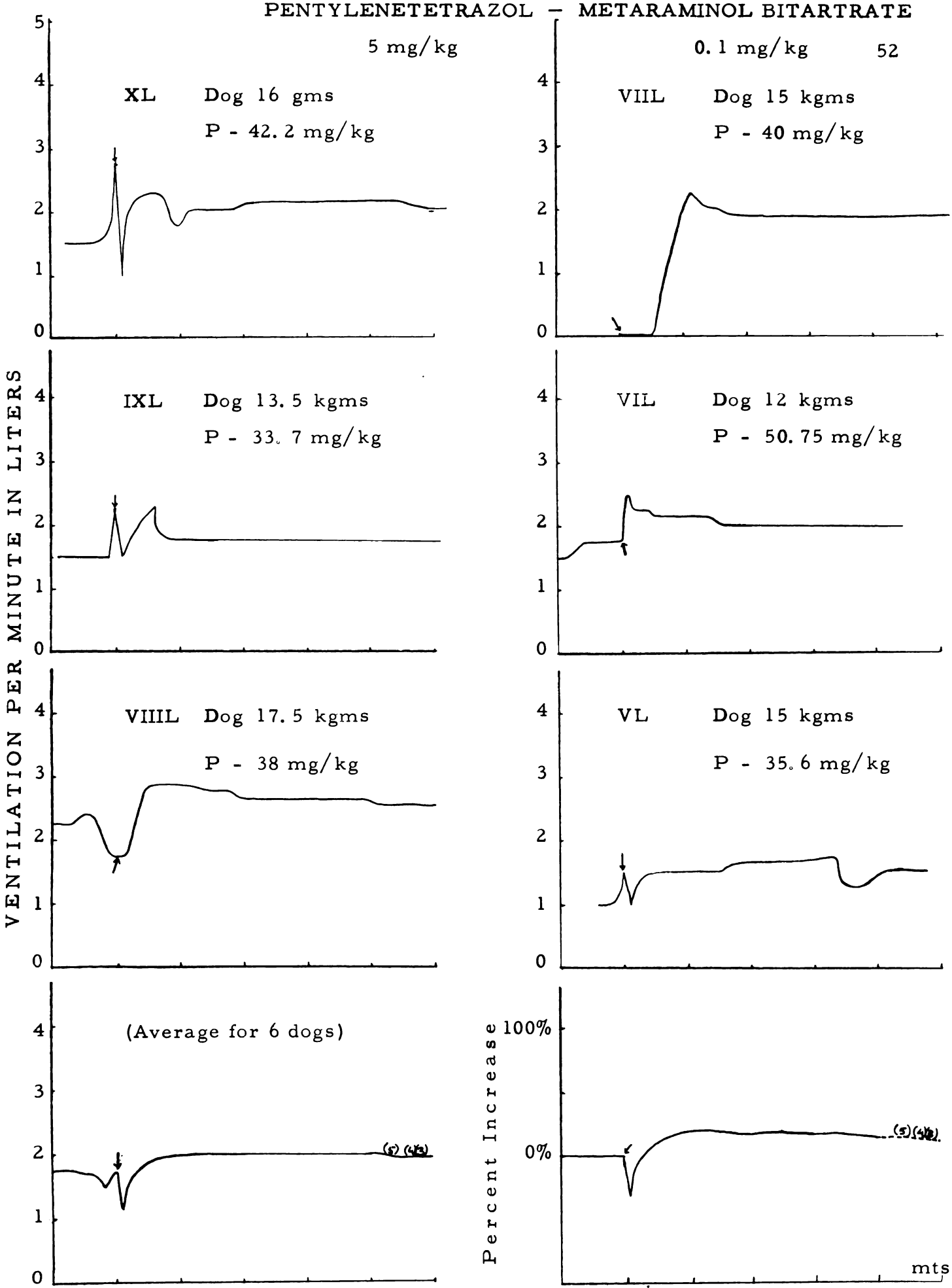

METHETHARIMIDE — PICROTOXIN
VENTILATION PER MINUTE IN LITERS
Percent Increase
XVI Dog 9 kgms
P - 40 mg/kg
Me
20 mg/kg
1 mg/kg
Pi
24.6 mg/kg
P
XIX Dog 13 kgms
P - 64.6 mg/kg
Me - 23 mg/kg
Me
3.5 mg/kg
P
XVII Dog 13.5 ggms
P - 43.5 mg/kg
Me - 21.75 mg/kg
XX Dog 12 kgms
P - 42.5 mg/kg
Me 21.25 mg/kg
XVIII Dog 10.5 kgms
P - 40 mg/kg
Me 20 mg/kg
XXI Dog 8 kgms
P - 40 mg/kg
Me 20 mg/kg
(Average for 6 dogs)
100%
0%
mts
-10 0 10 20 30 40 50


PICROTOXIN
1 mg/kg
XXII Dog 14.5 kgms
P - 45.5 mg/kg
XXIII Dog 14.5 kgms
P - 46.5 mg/kg
XXIV Dog 11.5 kgms
P - 41.8 mg/kg
(Average for 6 dogs)
METARAMINOL BITARTRATE
0.1 mg/kg
XXV Dog 9 kgms
P - 40 mg/kg
XXVI Dog 9 kgms
P - 40 mg/kg
XXVII Dog 13 kgms
P - 40 mg/kg
VENTILATION PER MINUTE IN LITERS
Percent Increase
100%
0%
(5)
(4)
-10
0
10
20
30
40
50 mts


PENTYLENETETRAZOL
5 mg/kg
XXVIII Dog 11.5 kgms
P - 41.75 mg/kg
AMPHETAMINE
2 mg/kg
XXXI Dog 13 kgms
P - 42.7 mg/kg
10 mg/kg
P
XXIX Dog 15 kgms
P - 50 mg/kg
XXXII Dog 9 kgms
P - 40 mg/kg
XXX Bitch 10.5 kgms
P - 40 mg/kg
XXXIII Bitch 8 kgms
P - 40 mg/kg
(Average for 6 dogs)
VENTILATION PER MINUTE IN LITERS
Percent Increase
100%
0%
mts


METHETHARIMIDE
PENTYLENETETRAZOL
5 mg/kg
51
XXXIV Dog 8.5 kgms
P - 42.4 mg/kg
Me - 21.2 mg/kg
Me
Pe
XXXVII Dog 9.5 kgms
P - 40 mg/kg
Pe
Pe
Me 20 mg/kg
XXXV Bitch 8.5 kgms
P - 49 mg/kg
Pe
Me
21.2 mg/kg
XXXVIII Bitch 11.5 kgms
P - 45 mg/kg
Pe
Me 22.5 mg/kg
XXXVI Dog 9 kgms
P - 45 mg/kg
Pe
Me 22.5 mg/kg
XXXIX Dog 7 kgms
P - 41 mg/kg
Pe
Me 20.5 mg/kg
(Average for 6 dogs)
Pe
Me
VENTILATION PER MINUTE IN LITERS
Percent Increase
100%
0%
Pe
Me
mts

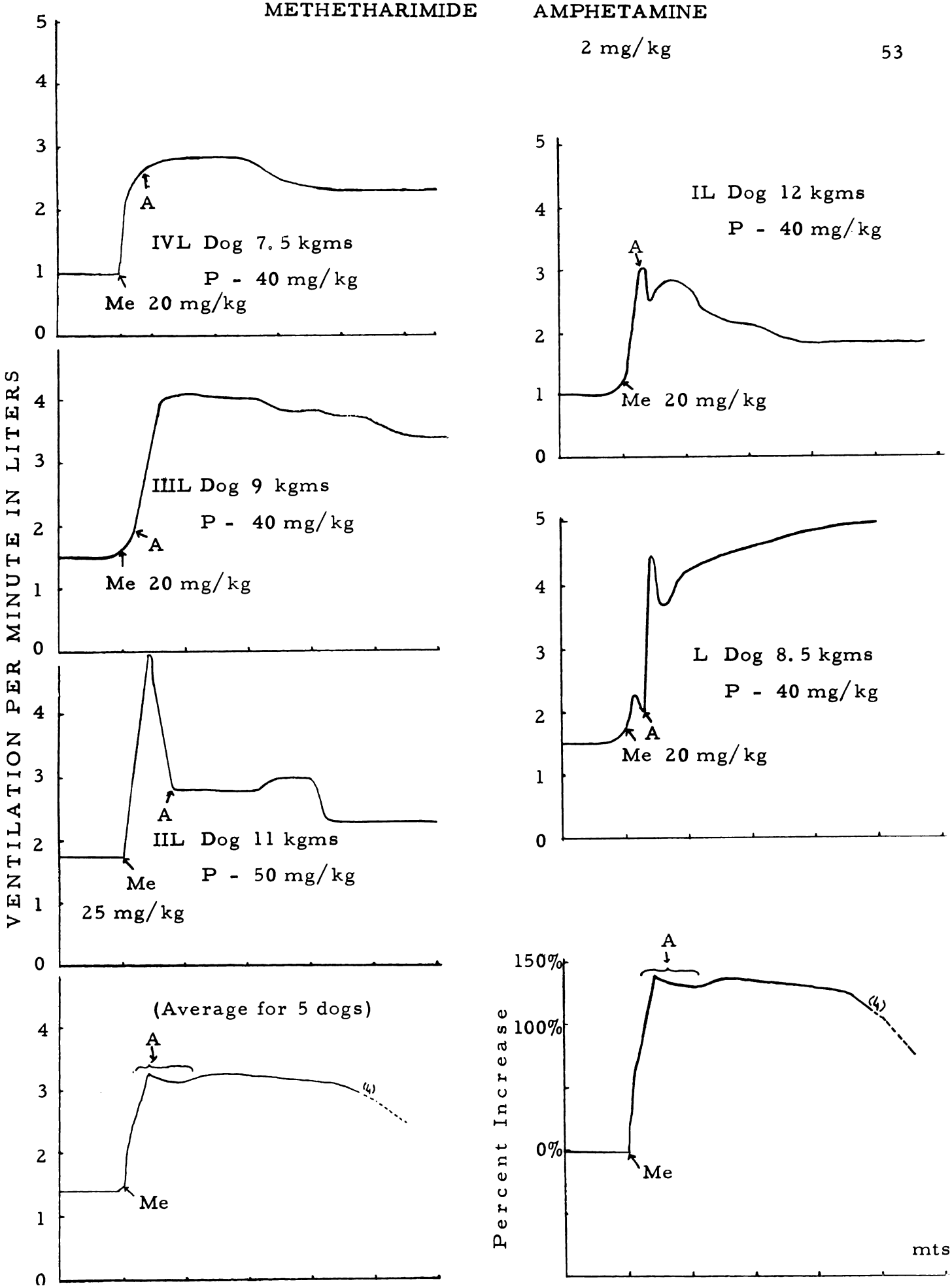
PENTYLENETETRAZOL – METARAMINOL BITARTRATE

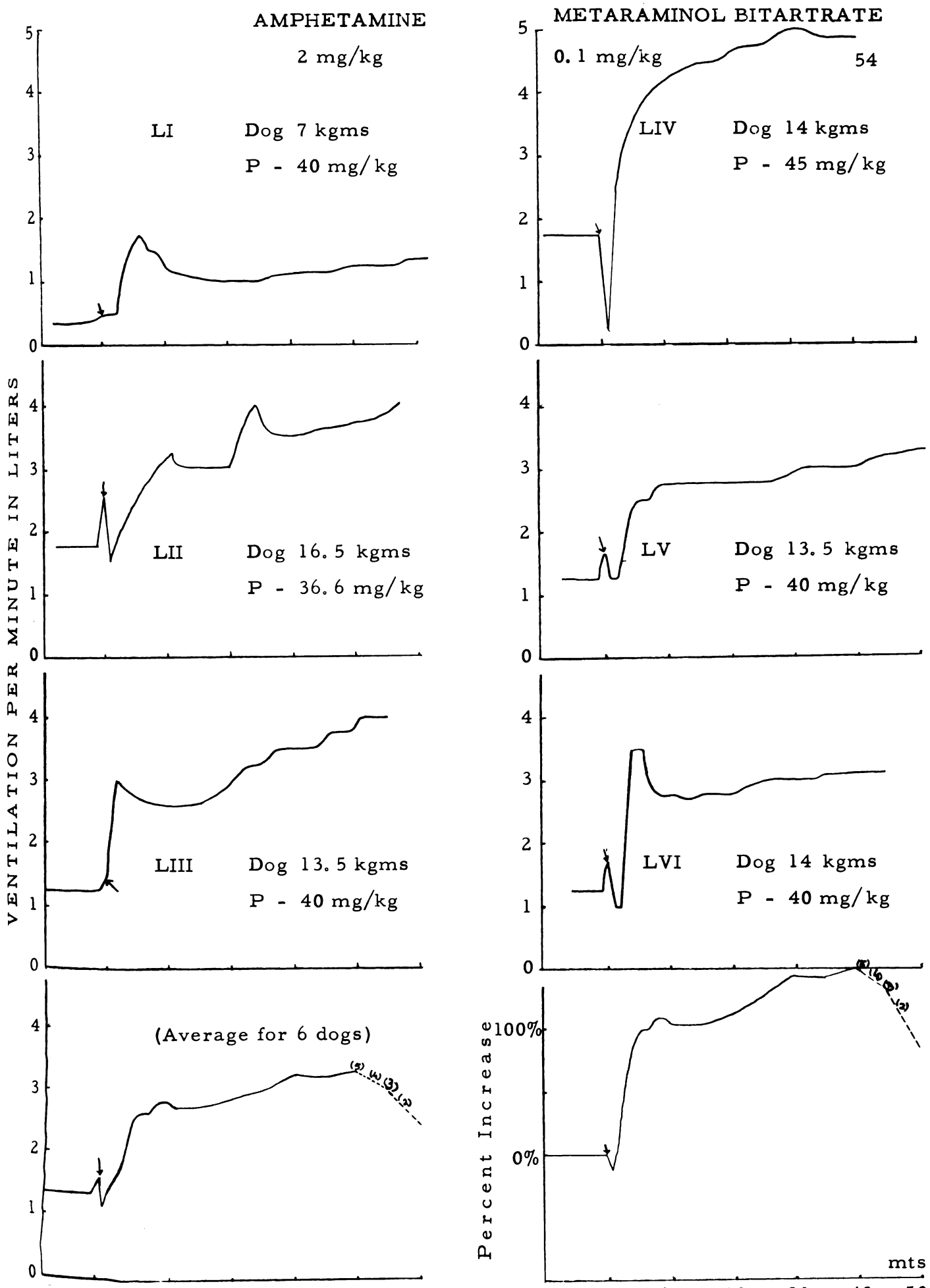


METHETHARIMIDE

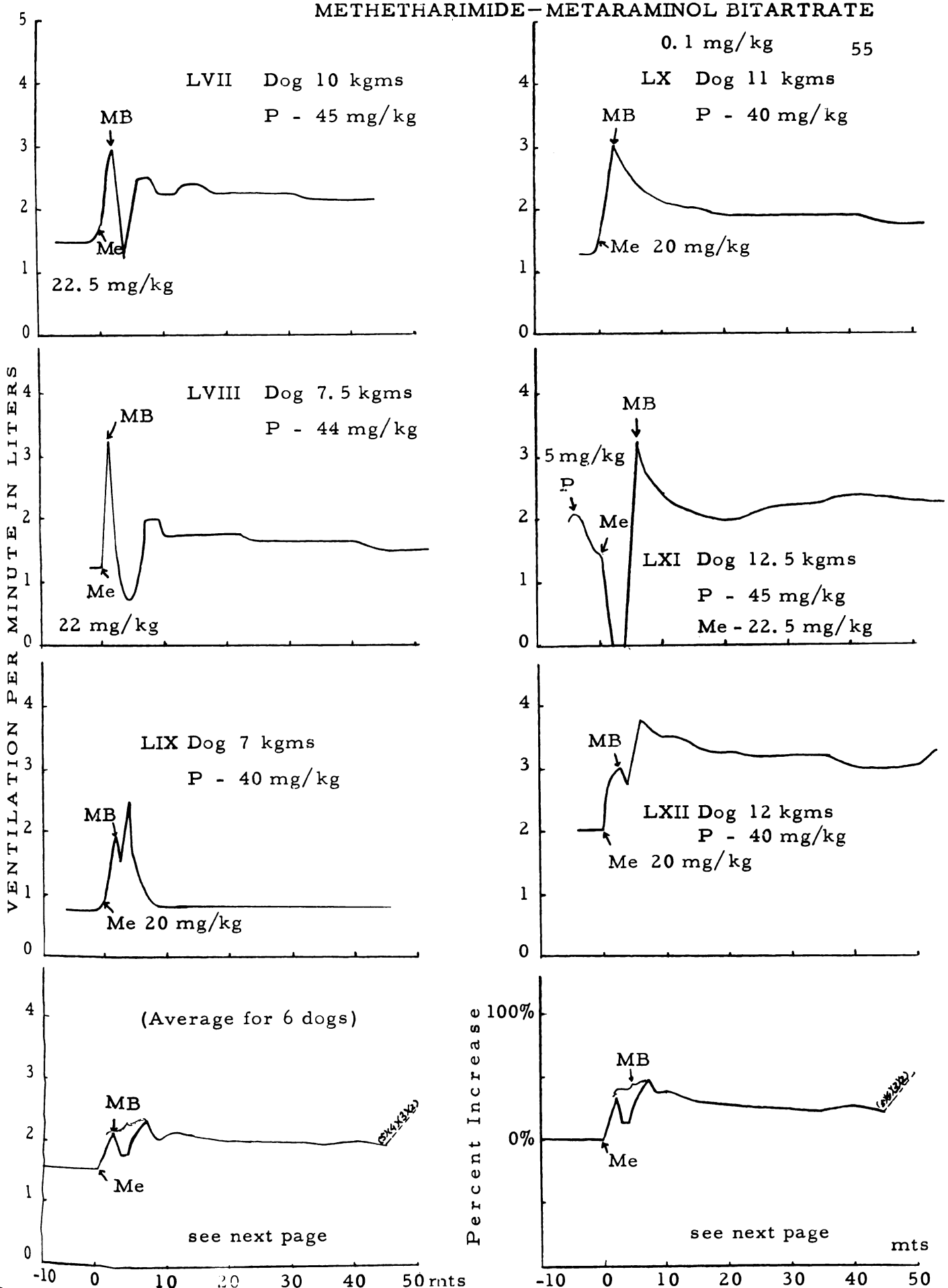
AMPHETAMINE

2 mg/kg

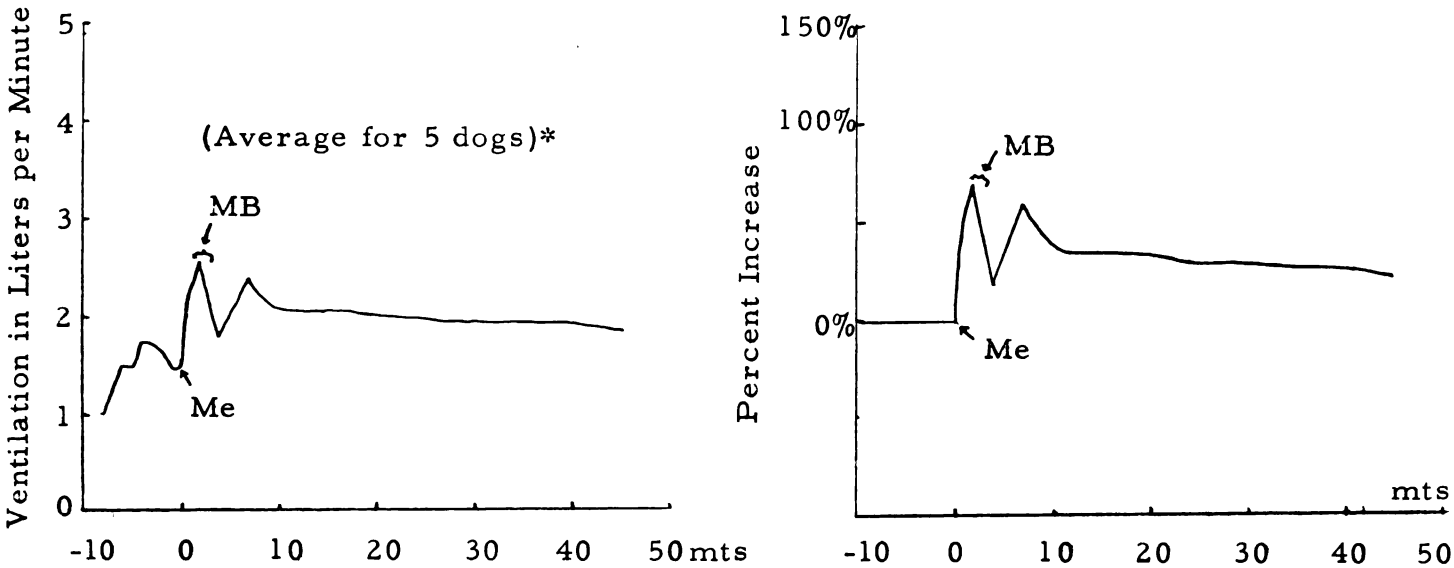



AMPHETAMINE
2 mg/kg
LI
Dog 7 kgms
P - 40 mg/kg
LII
Dog 16.5 kgms
P - 36.6 mg/kg
LIII
Dog 13.5 kgms
P - 40 mg/kg
(Average for 6 dogs)
METARAMINOL BITARTRATE
0.1 mg/kg
54
LIV
Dog 14 kgms
P - 45 mg/kg
LV
Dog 13.5 kgms
P - 40 mg/kg
LVI
Dog 14 kgms
P - 40 mg/kg
VENTILATION PER MINUTE IN LITERS
Percent Increase
100%
0%
mts
-10
0
10
20
30
40
50

METHETHARIMIDE–METARAMINOL BITARTRATE

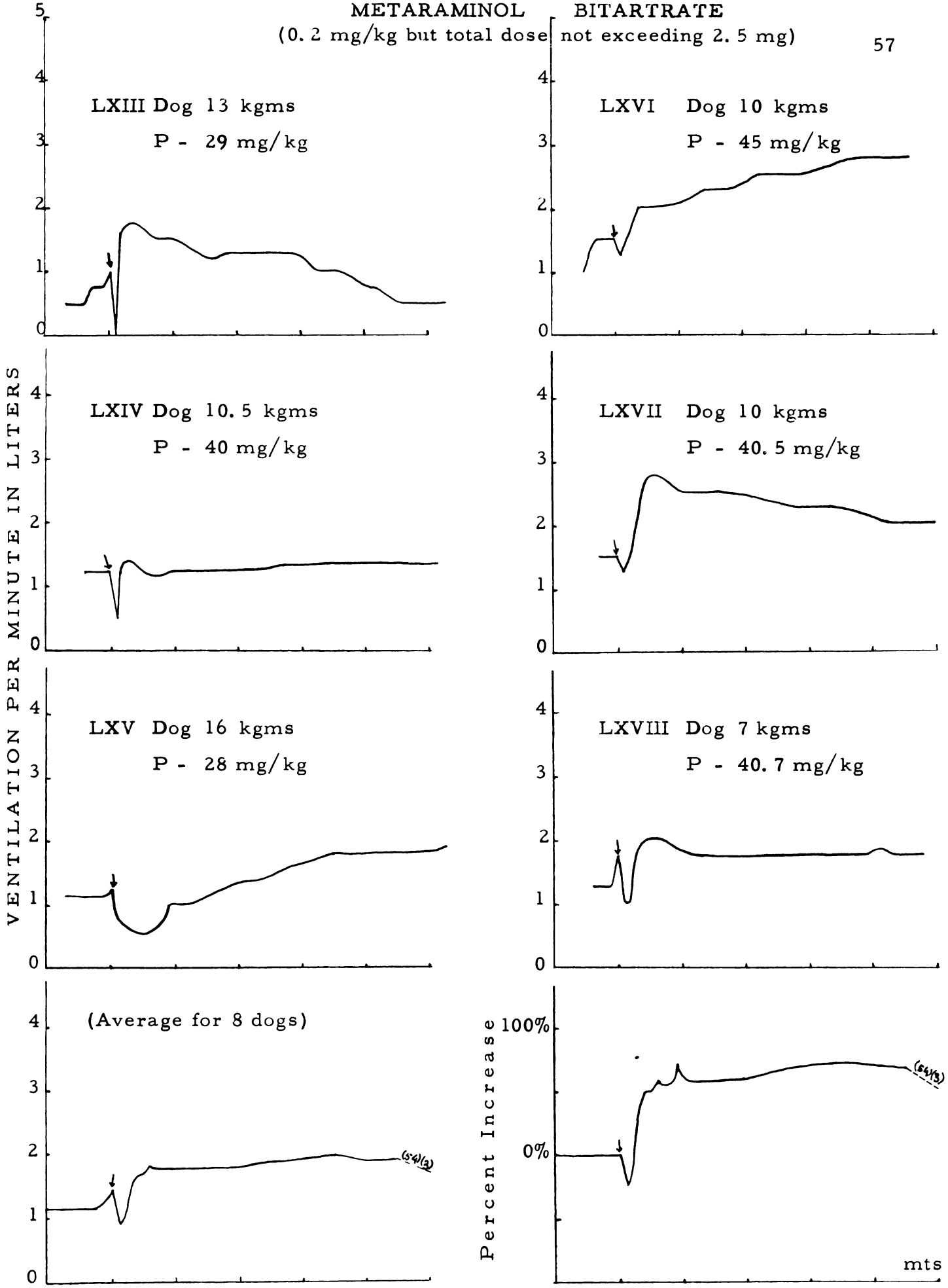


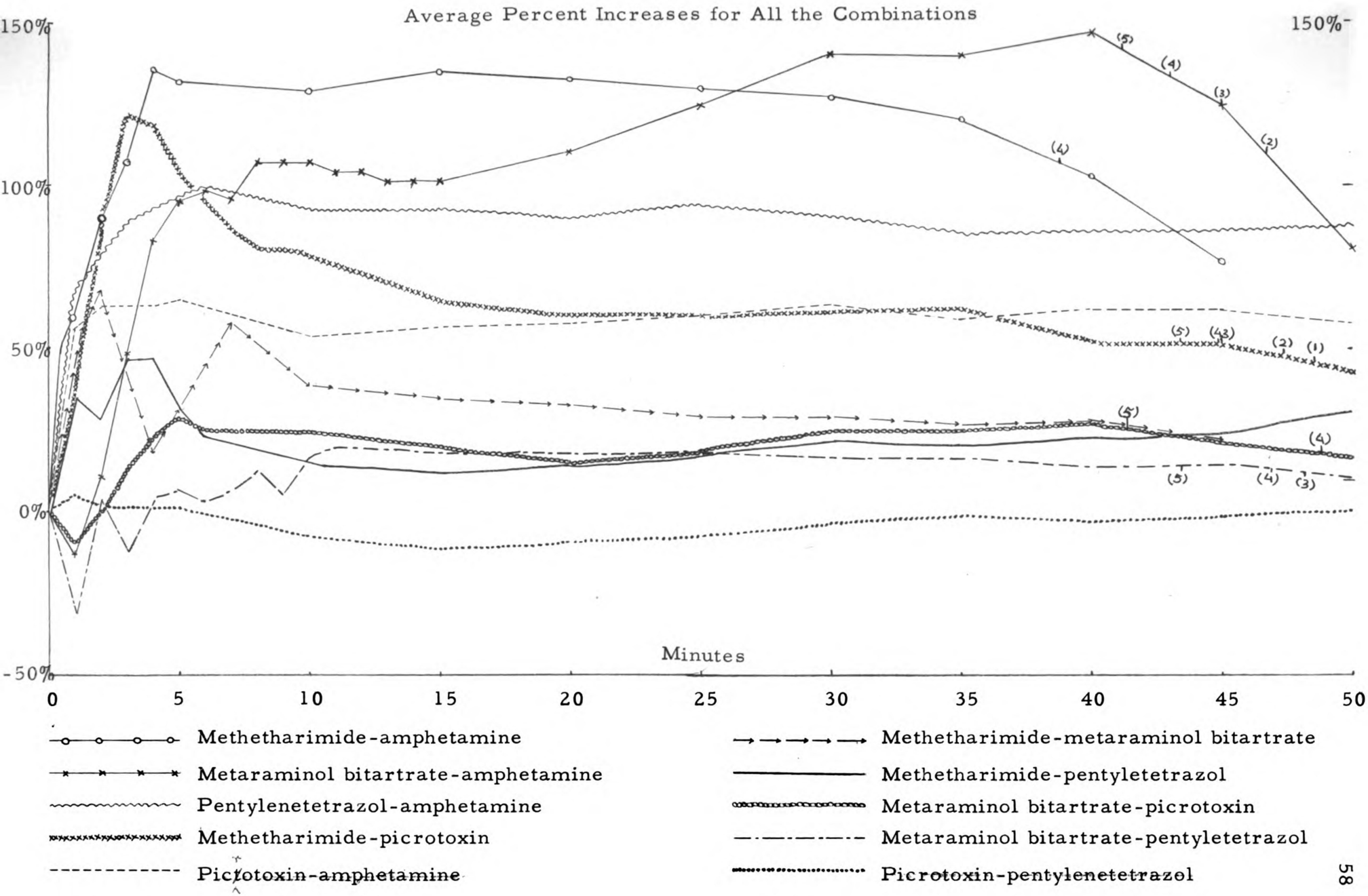
METHETHARIMIDE – METARAMINOL BITARTRATE

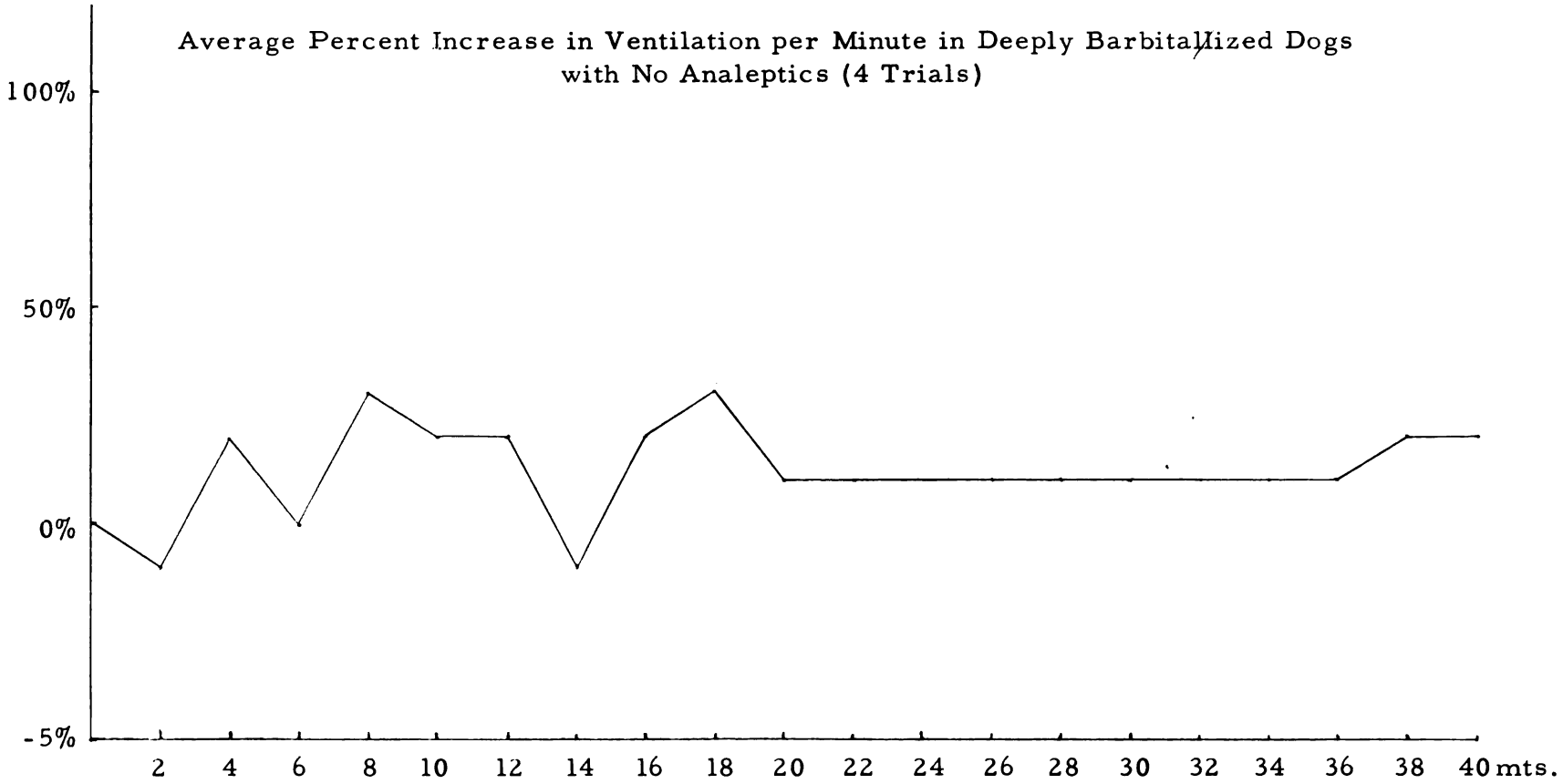


*These average and percentage increase graphs are for dogs LVII, LVIII, LIX, LX and LXII only. The dog No. LXI has been excluded because the condition under which the analeptic was administered was not exactly typical of others. In this case a second dose of pentobarbital 5 mg/kg was given only about 4 minutes prior to the analeptic while in others the pentobarbital was given 15-20 minutes before the analeptic.

METARAMINOL BITARTRATE
(0.2 mg/kg but total dose not exceeding 2.5 mg)




Average Percent Increases for All the Combinations
150%
100%
50%
0%
-50%
Minutes
0
5
10
15
20
25
30
35
40
45
50
(5)
(4)
(3)
(2)
(1)
Methetharimide-amphetamine
Metaraminol bitartrate-amphetamine
Pentylenetetrazol-amphetamine
Methetharimide-picrotoxin
Picrotoxin-amphetamine
Methetharimide-metaraminol bitartrate
Methetharimide-pentyletetrazol
Metaraminol bitartrate-picrotoxin
Metaraminol bitartrate-pentyletetrazol
Picrotoxin-pentylenetetrazol



By courtesy from Dr. Cairy

CHAPTER IV

DISCUSSION

1. Picrotoxin-Metrazol combinations--Picrotoxin directly or indirectly as stated in literature review stimulates the respiratory center in the medulla to increase ventilation in a barbitallized animal. It has a latent period of action of about 5-10 minutes duration. Pentylenetetrazol also has a similar but weaker medullary stimulant effect to increase ventilation. In barbitallized dogs it alone causes a quick 100 percent rise in ventilation which slowly drops down to a level of about 50 percent rise in ventilation rising again at about 40 minutes to a level of about 80 percent rise in ventilation then dropping quickly to a level of about 20 percent rise in ventilation (Cairy and Leash).

Thus what we expect from a combination of picrotoxin and pentylenetetrazol in a barbitallized dog is at least an initial rise of above 100 percent in the ventilation later maintained at a level somewhere above 50 percent rise in the ventilation for at least 40 minutes. What we observed in our results is an initial rise of 6 percent soon dropping down to a level of 9 percent fall in the ventilation, maintaining itself at a level between 1-11 percent fall in ventilation for about 45 minutes then hardly recovering to the 0 percent rise level. Observing such results in 3 dogs the mode of administration of combination was changed from mixing the two components in one syringe to injecting them one

after the other by the same needle. The 3 dogs receiving first pentylenetetrazol immediately followed by picrotoxin, ventilation level showed an initial rise of 13 percent later maintained between 3 percent fall to 5 percent rise giving a general impression of insignificant improvement in ventilation level if at all. The third set of 3 dogs receiving first picrotoxin followed by Metrazol gave a bit better results than the other two. It produced an initial rise in ventilation level of about 19 percent which all the time steadily went on rising to a level of about 70 percent rise in 50 minutes, touching at times even 80 percent rise in ventilation level, but this too is not quite the expected effect.

It is surely difficult to explain this poor performance of this combination. A physiological antagonism between these two drugs is hard to believe, and no chemical antagonism also is known so far. No precipitate could be observed when the two drugs were mixed in one syringe for administration, but it is possible that Metrazol forms a soluble chemical complex with picrotoxin making the combination ineffective or even harmful.

The slight improvements in second and third sets of dogs may be due to the quickly absorbed pentylenetetrazol or picrotoxin into the tissues before the second drug came into circulation to make the soluble chemical complex. It is assumed that the drug absorbed into tissues does not form such complex and is active. In the second set of dogs pentylenetetrazol was injected first and the volume injected

was usually less than 1 cc so it was injected in very little time immediately followed by picrotoxin solution. This gives much less time for pentylenetetrazol to be quickly absorbed by the tissues before it forms complex with picrotoxin, than what picrotoxin gets when it is injected first, because picrotoxin solution has a bulk of 2-4 cc usually, thus taking more time for injecting and so allowing more time for its quick absorption into tissues before the pentylenetetrazol comes into circulation to form the complex. This may also explain why the third set was still better than the second.

2. Picrotoxin-amphetamine combination--Amphetamine also stimulates medullary centers to increase ventilation, but its cardiovascular effects limit it a bit, and the effect observed in barbitallized dogs is a slow 100 percent rise in ventilation with no prominent initial peak. Thus in a combination with picrotoxin we can expect a slow initial rise reaching its first peak at about 8 minutes, i.e. after the latent period of action of picrotoxin. This level of ventilation may later be improved or maintained by amphetamine.

The result shows a peak rise in ventilation of 65 percent at 5 minutes which later is maintained at a level between 54-63 percent rise in ventilation up to 50 minutes. That combination could not raise the ventilation by 100 percent may be because both drugs are combined in half their therapeutic doses and the effect of these half doses is not synergistic but purely additive to give this moderate but maintained improvement in ventilation, and that no half of the drugs

was potent enough in itself to raise the ventilation by 100 percent at any point.

3. Picrotoxin-methetharimide combination--Methetharimide in barbitalized dogs produces an immediate rise in ventilation by 150 percent followed by rather prompt fall to a 60 percent rise level, sustained for at least 40 minutes sometimes showing another rise in ventilation at this time (Cairy and Leash). Thus we can expect from its combination with picrotoxin an initial peak rise in ventilation due to methetharimide during the latent period of action of picrotoxin, maintained later at a respectable level by picrotoxin and methetharimide both.

In the results a similar pattern is observed though the peak and the level maintained are not so high which again may be due to half the therapeutic doses of the drugs used. The theory that methetharimide due to its structural similarity to barbiturates antagonizes them by competing for the same substrate in the brain quite easily supports this, as the less the amount of methetharimide, the less it will compete with barbiturates, and less will be its effect. Picrotoxin as mentioned before does not act quite the same way so there is no synergism, and the effects of half doses of picrotoxin and methetharimide do not much push each other up, but yet the additive effect is quite respectable.

4. Metaraminol bitartrate--As the results show, causes an immediate fall of about 34 percent in the ventilation level followed by

a rapid rise to about 50 to 60 percent above the original level and then a progressive rise to up to 73 percent in about 35 minutes.

The initial drop in ventilation level seems to come reflexly from its cardiovascular effects. The subsequent improvement is not well explained. There may be possibility that metaraminol bitartrate like amphetamine is not only a sympathomimetic but also has some CNS--and especially medullary--stimulant effects though this has not yet been established.

5. Picrotoxin-metaraminol bitartrate--As expected, during the latent period of action of picrotoxin, metaraminol bitartrate tends to produce an initial fall in ventilation rate followed by a rapid rise and then more or less maintained at level, but the fall, the rapid rise and also the level maintained are quite a bit lower than the effects of the full doses of the individual drugs. This shows that the two halves of these two drugs do not support each other much, and fail to produce a full effect.

6. Pentylenetetrazol-amphetamine combination--Amphetamine is a sympathomimetic amine stimulating the cardiovascular system as well as the CNS. Barbiturates produce a considerable depression of the cardiovascular system even under controlled anesthetic conditions (Daniel et al., 1956). Amphetamine thus antagonizes barbiturates at CNS as well as cardiovascular system. Amphetamine is a long acting drug due to slow destruction and so also maintains a good ventilation level. Amphetamine alone does not produce a rapid improvement in

in the beginning, but pentylenetetrazol does so. Thus the combination produces a rapid rise in ventilation of about 100 percent subsequently maintained between 85-95 percent rise levels of ventilation. The result suggests that pentylenetetrazol and amphetamine do help each other in producing their effects ultimately producing a very respectable and more steady improvement in ventilation than either of these drugs in full doses alone could have produced. This favors the opinion of Weaver and Bunde (1960) that "cardiovascular system as well as the respiratory system should be considered when attempts are made to antagonize barbiturates."

7. Pentylenetetrazol-methetharimide combination--As mentioned before pentylenetetrazol is a medullary stimulant and methetharimide is a competitor with barbiturates for the same substrate in the brain. The combination is expected to behave more or less like picrotoxin-methetharimide combination. In the results it does give a similar pattern but with very poor improvement in ventilation. It produces an initial peak of up to 47 percent rise in ventilation which drops down to a 13 percent rise level in 6 minutes and is later maintained between 10-20 percent rise level for at least about 40 minutes. In the picrotoxin-methetharimide combination, if the initial peak was not affected by picrotoxin due to its latent period and was mostly due to the methetharimide, then in this pentylenetetrazol-methetharimide combination pentylenetetrazol has somehow considerably pulled down even the effect of methetharimide alone, at least at the peak and

probably later on too, and has provided a poor maintenance level. To explain this neither any physiological incompatability seems feasible nor any chemical one is known so far, but there may be a possibility of formation of a soluble chemical complex again, though there is no proof for it.

8. Pentylenetetrazol--metaraminol bitartrate combination--In this combination metaraminol bitartrate dominates on the cardiovascular effects, raises blood pressure and so reflexly lowers the ventilation by 30 percent initially, then raises it to about 20 percent above original level in about 10 minutes and maintains later between 10-20 percent rise levels. The combination does not look to be useful and the author feels inclined to say that pentylenetetrazol has affected metaraminol bitartrate too adversely, instead of helping it as it did with picrotoxin and methetharimide, though it is hard to say anything about the real phenomenon.

9. Amphetamine-methetharimide combination--Methetharimide as mentioned before produces an immediate rise of 150 percent in ventilation followed by a rather prompt fall to about 60 percent rise level above the original (Cairy and Leash) in barbitallized dogs. Amphetamine in similar conditions produces a slow 100 percent rise in ventilation (Cairy and Leash). Thus what we expect in combination is an immediate rise due to methetharimide later maintained by amphetamine. The result shows an immediate rise of 136 percent in ventilation later maintained between 103-136 percent rise levels of

ventilation for at least 40 minutes. The result looks superior to what could be obtained by either of these two drugs alone in full doses. This suggests that the two halves of the drugs have somehow pushed up each other's effects and again confirms the ideas of Weaver and Bunde (1960).

10. Amphetamine-metaraminol bitartrate combination--From the behaviors of these two drugs in barbitallized dogs as mentioned before one should expect first a drop in ventilation reflexly due to the metaraminol bitartrate's effect on cardiovascular system, then a steady rise due to metaraminol bitartrate and amphetamine both to at least respectable levels. As both are sympathomimetic amines so one can expect them to help each other in their action. This comes out true when we see the result which shows an initial drop of 13 percent below original ventilation level then a quick rise to 95 percent above original ventilation level in the next 4 minutes and then a gradual rise all the way reaching a maximum ventilation level of 150 percent rise above original at about 40 minutes. This too appears to be a better result than either of these drugs could produce alone even in full doses.

11. Methetharimide-metaraminol bitartrate combination--In this combination as methetharimide is injected first one should expect an initial immediate peak in ventilation due to it, followed by an abrupt fall as soon as metaraminol bitartrate is injected as it would do so reflexly by raising the blood pressure. This fall should then be

followed by a gradual but steady rise in ventilation level mostly due to metaraminol bitartrate. The result accordingly shows a quick initial peak rise of 68 percent then a fall to 19 percent rise level followed by another peak of 58 percent rise level, then a fall to about 39 percent level and then maintained at a level between 22-39 percent rise above the original ventilation level. Thus the pattern of the result is more or less as expected but the improvement in the ventilation is not even half as good as with methetharimide and amphetamine combination although metaraminol bitartrate also is a sympathomimetic amine like amphetamine.

This now suggests that the effect of amphetamine with methetharimide is not merely additive but is synergistic while such is not the case with metaraminol bitartrate and methetharimide, instead it looks that even metaraminol bitartrate itself has not helped ventilation to the extent that could have been expected from it alone.

SUMMARY

All the possible paired combinations of picrotoxin, pentylenetetrazol, amphetamine, methetharimide and metaraminol bitartrate, and metaraminol bitartrate alone were tried for their efficiency to improve ventilation in deeply barbitalized dogs and were found to be in the following descending order of efficacy:

Methetharimide - Amphetamine

Amphetamine - Metaraminol bitartrate

Amphetamine - Pentylenetetrazol

Methetharimide - Picrotoxin

Amphetamine - Picrotoxin

Metaraminol bitartrate

Methetharimide - Metaraminol bitartrate

Methetharimide - Pentylenetetrazol

Metaraminol bitartrate - Picrotoxin

Metaraminol bitartrate - Pentylenetetrazol

Pentylenetetrazol - Picrotoxin

It was observed that most combinations with amphetamine were very good while most combinations with pentylenetetrazol were quite poor. In between these two extremes were methetharimide, metaraminol bitartrate and picrotoxin in the descending order.

Metaraminol bitartrate has a blemish of first depressing the ventilation for a very short time before improving it steadily and markedly, but this blemish becomes less dangerous due to the simultaneous improvement of the cardiovascular system.

Methetharimide sometimes seems to cause peculiar straining inspirations which continue till the animal recovers to normal senses. Methetharimide combinations showed the best awakening properties.

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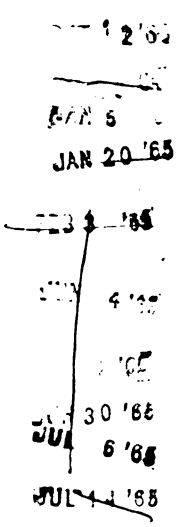
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