AN EXPERIMENTAL STUDY OF THE EFFECTS OF RESPIRATORY STIMULANTS IN ANIMALS UNDER PENTOTHAL SODIUM ANESTHESIA *

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ONE of the principal objections to the use of barbiturates for surgical anesthesia has been the accompanying marked respiratory depression. The desirability of having available an effective respiratory stimulant for use in case of need is obvious. The present study was made to determine the efficacy of five preparations that have been recommended for stimulating respiration. It was hoped that one of the drugs could be used successfully to combat respiratory depression and poisoning from the shorter acting barbiturates, especially pentothal sodium. The experimental animals were dogs, cats and rabbits. The drugs used were coramine (pyridine betacarbonic acid diethylamide), metrazol (pentamethylenetetrazol), picrotoxin ($C_{30}H_{34}O_{13}$), alphâ-lobeline ($C_{22}H_{27}O_2N$) and neospiran (orthophthalic acid-bis-diethylamide).

LITERATURE

Killian (1) in his report on the use of coramine as an antagonist in avertin narcosis suggested that coramine exerts an almost specific action in stimulating the depressed respiration. Intravenous injection of coramine gave a profound but rather transitory effect on respiration while intramuscular injection gave a slower and more prolonged action. "The results were not a complete recovery of consciousness from the deepest sleep, but rather the overcoming of a threatening condition into a state of sleep from danger."

Maloney and Tatum (2) reported coramine to be more effective than metrazol in counteracting the depressing action of morphine, urethane, chloral hydrate, tribromethanol and ether. They also suggested that neither drug is of value in counteracting depression due to the barbituric acid derivatives. Veal and Hamilton (3), working with experimental animals anesthetized with lethal doses of evipal soluble, found

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that intravenous and intracardiac injections of coramine, metrazol, picrotoxin and alpha-lobeline failed at resuscitation. Maloney and Tatum (2) reported the results of experiments in which caffeine, strychnine, metrazol and coramine were used in the treatment of animals poisoned by avertin and other narcotic substances. Coramine proved to be the most efficient and the safest of the drugs used. Wood (4) found, from observation of 83 clinical cases, that coramine is a definite stimulant to respiration and circulation in cases of depression by avertin narcosis or surgical shock. He found that the toxicity of coramine was low and that large doses could be repeated intravenously.

Clemmesen (5) used coramine either intravenously or intramuscularly in 69 cases in which the patient was admitted to the hospital for treatment following poisoning by gas, barbituric acid preparations, morphine and other drugs. He expressed the opinion that the majority of the patients derived some benefit from this treatment but the patients poisoned by gas or morphine responded much better to coramine than did those who had been poisoned by a barbiturate.

Maloney (6) reported from experiments on rats and rabbits narcotized with barbital and treated with caffeine, coramine or metrazol that these substances are capable of accentuating the depressant action of the barbiturates under certain conditions. Stimulating amounts of coramine and metrazol given in single or fractional doses to barbitalized rabbits caused transitory arousal with certain doses and death in depression with other doses; but in every instance coramine or metrazol, when combined with barbital, increased the duration of narcosis over that of the controls and caused some deaths.

Peters and Visscher (7), working with a modified Knowlton and Starling heart-lung preparation, found that cardiac failure may be produced by some drugs reputed to be cardiac tonics. While other drugs apparently exert no direct action on the heart at all, metrazol produced either no effect on the heart or only a slight acceleration. Coramine caused cardiac dilatation with an unchanged or diminished output and decreased efficiency. The decrease in the work output was entirely owing to loss of efficiency.

Maloney, Fitch and Tatum (8), working with dogs anesthetized with amytal, pernoston and pentobarbital sodium, found picrotoxin to be effective as an antidote. They recommended doses of 5 to 10 mg. of picrotoxin to be given intravenously to the depressed dog every five to twenty minutes. Koppanyi, Linegar and Dille (9) found that metrazol and picrotoxin produce an awakening effect in man if the minimal anesthetic dose of barbital sodium or pentobarbital sodium is given, but when excessive doses have been given to animals, administration of the stimulants may be pushed to the point of convulsions without awakening the animal.

King, Hosmer and Dresbach (10) reported on work dealing with the action of intravenous injections of alpha-lobeline in the dog, cat, mon-

key, rabbit and man during depression from amytal, morphine, barbital, ether, carbon monoxide, carbon dioxide and increased intracranial pressure. They found that respiration can be increased tremendously in the intact animal or man in light or moderate anesthesia. Arterial pressure is raised in moderately depressed animals. In deeply depressed animals arterial pressure can be lowered by doses of alphalobeline which in lesser degrees of depression would stimulate respiration and increase the blood pressure. In the deeply depressed animal the respiratory stimulation is likely to fail altogether and a fatal fall in blood pressure can be obtained easily.

Haffner, Schellong and Baetzner (11) found neospiran to be of value in combating depressed respiration caused by narcotics and reported beneficial effects in patients suffering from surgical shock and circulatory collapse.

METHODS AND RESULTS

Kymographic records were made of the respiratory rate by means of a pneumograph. When the blood pressure was taken, one of the femoral arteries was cannulated and the blood pressure was recorded by means of a mercury manometer and other standard equipment. To obtain the electrocardiograms a Sanborn cardiette was used.

It is well known that certain species of animals may respond to a given drug in a manner different from the response of another species. In order to avoid such an eventuality in the study of the drugs in question, three different species were used. Dogs and cats anesthetized with pentothal sodium were used to determine the effect of each drug on the respiratory rate. The effect of each drug on the blood pressure, respiratory rate and electrocardiogram was observed in dogs under sodium isoamylethyl-barbiturate (sodium amytal). The analeptic potency of all the drugs was determined in rabbits under pentothal sodium anesthesia.

The minimal lethal intravenous dose of pentothal sodium was determined for dogs and rabbits and the minimal convulsive dose of the other drugs was ascertained for each species in the absence of anesthesia (Table 1).

A large series of observations was made with each drug on the different species of animal used, but in order to conserve space only representative data showing the characteristic action of each of the various drugs will be presented. An attempt was made to select data illustrating the maximal and minimal effects of each drug in each series of experiments.

Coramine.—The effect of coramine on dogs and cats anesthetized with pentothal sodium shows that dogs whose respirations have not been depressed seriously by the anesthetic agent receive some stimulation after coramine has been administered intravenously. Dogs whose respiratory rates were depressed by the anesthetic agent received no

TABLE 1

MINIMAL LETHAL DOSES OF PENTOTHAL SODIUM AND MINIMAL CONVULSIVE DOSES OF THE OTHER DRUGS USED

Minimal lethal dose	Pentothal sodium	5 dogs	50 mg./kg.
Minimal lethal dose	Pentothal sodium	15 rabbits	35 mg./kg.
Minimal convulsive dose	Coramine	4 dogs 4 cats	20 mg./kg. 14 mg./kg.
Minimal convulsive dose	Metrazol	4 dogs 4 cats	8 mg./kg. 6 mg./kg.
Minimal convulsive dose	Alpha-lobeline	4 dogs 4 cats	0.5 mg./kg. 0.5 mg./kg.
Minimal convulsive dose	Neospiran	4 dogs 4 cats	4 mg./kg. 2 mg./kg.
Minimal convulsive dose	Picrotoxin	4 dogs 4 cats	0.2 mg./kg. 0.2 mg./kg.

benefit from the intravenous administration of coramine, the respiratory rates remaining essentially the same. One dog died, apparently of cardiac failure, within five minutes after the administration of coramine.

Satisfactory records of respiratory movements could not be made on cats, owing to violent seizures of sneezing which almost invariably occurred after the administration of coramine (Table 2).

Metrazol.—Animals anesthetized with pentothal sodium and then given metrazol demonstrated results very similar to those in animals which received coramine. The lightly anesthetized animals showed

TABLE 2

EFFECT ON RESPIRATION OF DIFFERENT DOSES OF CORAMINE GIVEN INTRAVENOUSLY TO DOGS AND CATS DURING PENTOTHAL SODIUM ANESTHESIA

Animal	Pentothal Sodium mg./kg.	Coramine, mg./kg.	Control Respiratory Rate	Respiratory Rate After Coramine				Remarks
				Immediate	1 min.	5 min.	10 min.	
Dog	35	50	12	Cessation	15	22		Nausea and vomiting 15 minutes after coramine
Dog	35	50	6	Cessation, 55 seconds	7	6	7	
Dog	35	10	10	Cessation, 50 seconds	9			Breathed for 2 minutes, then stopped. Animal died in spite of artificial respiration
Cat	40	40	15	Sneezing				Sneezing violently
Cat	30	16	16	Sneezing	16			Violent coughing and sneezing after 1 minute
Cat	30	10	12	Stimulation	16	16		

some degree of respiratory stimulation after metrazol was given. An increased depression was apparent after administration of metrazol in the more deeply depressed animals (Table 3).

TABLE 3

EFFECT ON RESPIRATION OF DIFFERENT DOSES OF METRAZOL GIVEN INTRAVENOUSLY TO DOGS AND CATS DURING PENTOTHAL SODIUM ANESTHESIA

Animal	Pentothal Sodium, mg./kg.	Metrazol, mg./kg.	Control Respiratory Rate	Respiratory Rate After Metrazol				Remarks
				Immediate	1 min.	5 min.	10 min.	
Dog	30	16	11	None	18	15	17	
Dog	46.5	5	5	None	4	3	4	
Dog	40	15	8	8	5	5	4	
Cat	20	15	14	None	15	12		Sneezing 45 minutes after metrazol
Cat	30	20	19		22	15	15	Moved during venipuncture
Cat	30	20	11	Cessation	16	13	13	

Alpha-lobeline.—Alpha-lobeline produced more respiratory stimulation in animals anesthetized with pentothal sodium than did any of the other drugs used. In the lightly anesthetized animals definite hyperpnea developed immediately after the administration of the drug. In the animals whose respirations were depressed from the anesthetic drug, further depression was produced by the action of alpha-lobeline. In one animal respiratory arrest developed after the administration of alpha-lobeline. Artificial respiration was required for forty minutes before the animal was able to breathe (Table 4).

Neospiran.—Neospiran produced some respiratory stimulation in lightly anesthetized animals, while deeply depressed animals received

TABLE 4

EFFECT ON RESPIRATION OF ALPHA-LOBELINE GIVEN INTRAVENOUSLY TO DOGS AND CATS DURING PENTOTHAL SODIUM ANESTHESIA

Animal	Pentothal Sodium, mg./kg.	Alpha-Lobeline, mg./kg.	Control Respiratory Rate	Respiratory Rate After Alpha-Lobeline				Remarks
				Immediate	1 min.	5 min.	10 min.	
Dog	50	0.6	6	Increase in depth	12			Increase lasted 45 seconds
Dog	50	0.6	5	4 quick breaths	5	5		
Dog	30	0.5	4	Cessation				Artificial respiration required for 40 minutes
Cat	33	0.5	18	Immediate response	58	34		Increased depth for 30 seconds
Cat	33	0.5	34	Immediate response	66			Increased depth for 30 seconds

no benefit to respiration even though muscular tremors and convulsions were produced. Cheyne-Stokes type of respiration was noted in the majority of animals that received neospiran (Table 5).

TABLE 5

EFFECT ON RESPIRATION OF DIFFERENT DOSES OF NEOSPIRAN GIVEN INTRAVENOUSLY TO DOGS AND CATS DURING PENTOTHAL SODIUM ANESTHESIA

Animal	Pentothal Sodium, mg./kg.	Neospiran, mg./kg.	Control Respiratory Rate	Respiratory Rate After Neospiran				Remarks
				Immediate	1 min.	5 min.	10 min.	
Dog	25	4	11	Cessation, 72 seconds	44	9	10	
Dog	25	3	38	Cessation, 70 seconds	16	26	48	Tremor, muscular spasm, salivation
Dog	30	5	10	Cessation, 30 seconds	10	8	9	Cheyne-Stokes respiration immediately after neospiran. Persisted for 13 minutes
Cat	30	5	15	Depth increased	35	28	12	Sneezing 15 minutes after stimulant was given
Cat	30	10	26	Convulsion			25	Convulsions lasted 10 minutes. Profuse salivation

Picrotoxin.—No stimulation of respiration was observed in a group of animals which received picrotoxin after an anesthetic dose of pentothal sodium had been given. Convulsions were noted as long as twenty-five minutes after the picrotoxin had been administered (Table 6).

TABLE 6

EFFECT ON RESPIRATION OF DIFFERENT DOSES OF PICROTOXIN GIVEN INTRAVENOUSLY TO DOGS AND CATS DURING PENTOTHAL SODIUM ANESTHESIA

Animal	Pentothal Sodium, mg./kg.	Picrotoxin, mg./kg.	Control Respiratory Rate	Respiratory Rate After Picrotoxin				Remarks
				Immediate	1 min.	5 min.	10 min.	
Dog	30	0.2	21	None	15	14	14	25 minutes after picrotoxin was given, the animal had a violent prolonged convulsion
Dog	30	0.1	17	None	15	13	12	Generalized muscular twitching 1 hour after picrotoxin was given
Dog	30	0.2	10	None	9	10	14	Convulsion 20 minutes after picrotoxin was given
Cat	30	0.2	11	None	11	11	11	
Cat	30	0.3	12	Violent sneezing				
Cat	30	0.5	18	None	19	17	15	50 minutes later the animal was spastic and hyperirritable

In addition to the experiments already described, a series of observations was made on the effect of appropriate intravenous doses of each drug on the blood pressure, respiration and the electrocardiogram of dogs anesthetized with sodium amytal. With the exception of alphalobeline, which produced a marked increase, all the drugs caused a decrease in blood pressure. The effect of all the drugs on the respiration was similar to the results with animals under pentothal sodium anesthesia. The electrocardiogram was not altered significantly by any of the drugs used (Table 7).

TABLE 7

THE EFFECTS OF ALPHA-LOBELINE, CORAMINE, METRAZOL, NEOSPIRAN AND PICROTOXIN ON BLOOD PRESSURE, RESPIRATION, AND THE ELECTROCARDIOGRAM IN THE DOG DURING ANESTHESIA WITH SODIUM ISOAMYLETHYLBARBITURATE (SODIUM AMYTAL) 50 MG./KG.

Dog No.	Wt., kg.	Drug, mg./kg.	Control Blood Pressure	Blood Pressure Immediately After Drug	Control Respiratory Rate	Respiratory Rate After Drug (min.)			Remarks
						1	5	10	
18	10	Alpha-lobeline, 0.25	165	280+	18	—	—	—	Electrocardiogram not taken
24	15	Alpha-lobeline, 1	123	136	21	Short increase lasting 10 sec.	11	11	No change in electrocardiogram
22	33	Coramine, 50	130	90	7	Immediate cessation	5	7	Dog remained anesthetized all day without more sodium amytal
17	23.6	Coramine, 25	146	121	26	23	15	—	No change in electrocardiogram
25	22	Metrazol, 10	140	110	45	110	—	—	Anesthesia so light before metrazol that dog moved on slight stimulation. No change in electrocardiogram
23	25.8	Neospiran, 15	138	115	18	Cessation	44	—	Blood pressure 90, 2 min. after stimulant. No change in electrocardiogram
27	13.5	Picrotoxin, 0.2	155	144	8	8	11	11	No change in electrocardiogram

Analeptic potency.—Certain of the drugs under investigation have been used to hasten recovery from deep anesthesia with barbiturates. It seemed desirable to determine the analeptic potency of each of the drugs on a series of rabbits. Each series of rabbits was anesthetized with pentothal sodium, after which the drug to be tested was given intravenously and the time required for the animals to assume an upright position was recorded. In every series the average recovery time of the rabbits that received one of the test drugs was greater than the recovery time of the controls that had received only pentothal sodium (Table 8).

TABLE 8

AVERAGE RECOVERY TIME OF RABBITS ANESTHETIZED WITH PENTOTHAL SODIUM, 35 MG. PER KILOGRAM OF BODY WEIGHT FOLLOWING INJECTIONS OF CORAMINE, NEOSPIRAN, METRAZOL, PICROTOXIN AND ALPHA-LOBELINE

	Number of Rabbits	Maximal Recovery Time, minutes	Minimal Recovery Time, minutes	Average Recovery Time, minutes
Controls	11	125	25	66.6
Followed by coramine 20 mg. per kilogram body weight	11	100	38	79.7
Anesthetic mixed with coramine 10 mg. per kilogram body weight	13	106	50	81.4
Followed by neospiran 10 mg. per kilogram body weight	11	113	67	94.8
Followed by metrazol 15 mg. per kilogram body weight	10	93	43	75.0
Followed by picrotoxin 0.2 mg. per kilogram body weight	11	110	40	82.1
Followed by alpha-lobeline 0.5 mg. per kilogram body weight	10	125	73	98.2

COMMENT

It has been apparent that the degree of respiratory stimulation after the administration of each of the drugs was dependent on the state of respiratory depression produced by the anesthetic agent. In the absence of anesthesia or in the lightly anesthetized animal an increase in the rate of respiration followed the injection of all the drugs but in the presence of a severely depressed respiration, each of the drugs caused a further depression and in many instances complete cessation of respiration. Consequently it is obvious that drugs that are effective only when not needed are of little practical value to the anesthetist.

CONCLUSIONS

1. Coramine, metrazol, picrotoxin, neospiran and alpha-lobeline are all convulsant drugs.
2. All the afore-named drugs are capable of producing varying degrees of respiratory stimulation in normal animals. The degree of respiratory stimulation produced with alpha-lobeline in normal animals is much greater than that obtained from the other drugs.
3. All the drugs produce some degree of respiratory stimulation in lightly anesthetized animals.
4. The drugs show almost no respiratory stimulating effects on animals deeply anesthetized with pentothal sodium or sodium amytal.
5. Depression often is increased after the administration of any of the stimulating drugs to animals deeply anesthetized with pentothal sodium or sodium amytal.
6. Cheyne-Stokes type of respiration often develops after the administration of neospiran to the anesthetized animal.

7. Blood pressure decreases immediately after the administration of coramine, metrazol or neospiran to the anesthetized animal. Alpha-lobeline produces an immediate increase in blood pressure when administered intravenously to the anesthetized animal, although on occasion respiration fails and the blood pressure of the anesthetized animal decreases rapidly. Picrotoxin causes very little change in the blood pressure.

8. Picrotoxin is capable of causing a convulsion to appear in a dog, which has been anesthetized previously with pentothal sodium, as long as twenty-five minutes after the drug has been given.

9. In each group of animals receiving one of the convulsant drugs, after the minimal lethal dose of pentothal sodium, the recovery time was lengthened over that of the controls.

10. It is impossible to give a sufficient quantity of coramine in mixed solution with a minimal lethal dose of pentothal sodium to prevent deep narcosis from developing.

11. The convulsant used caused no demonstrable change in the electrocardiogram of dogs anesthetized with sodium amytal.

Coramine, metrazol, picrotoxin, alpha-lobeline and neospiran are without value in treating severe depression caused by pentothal sodium anesthesia in dogs, cats or rabbits.

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