

NEUROMUSCULAR AND GANGLIONIC BLOCKING ACTION OF THIAMINE AND ITS DERIVATIVES

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THERE have been several reports in the past decade indicating that thiamine in large doses intravenously or intramuscularly can cause vascular collapse (1, 2, 3). The vascular failure generally has been attributed to an anaphylactic reaction. A more recent report attributes the fall in blood pressure to release of histamine and to inhibition of cholinesterase (4). There is also a brief report that thiamine is capable of causing ganglionic block (5). These pharmacologic actions of thiamine should be of interest to anesthetists since many surgical patients receive as a routine large parenteral doses of thiamine.

Thiamine by virtue of its thiazolium ring structure is a quaternary ammonium compound and thus related, although remotely, to compounds which are neuromuscular and ganglionic blocking agents. Indeed, the neuromuscular blocking capacity of thiamine has been substantially established (4, 6, 7, 8). The present investigation is an attempt to relate the fall in blood pressure following thiamine to ganglionic block and further to show the temporal relationship between the neuromuscular and ganglionic block. Acetylthiamine, oxythiamine, and pyriethiamine were also studied to learn if these pharmacological effects were common to homologous chemical compounds.

METHODS

The dogs and cats in these experiments were anesthetized with Dial-Urethane 0.6 ml./kg. intraperitoneally. The right vagus trunk together with the sympathetic trunk was isolated and the carotid artery prepared for blood pressure recording. The sciatic nerve was then dissected and cut, the peripheral end reserved for stimulation of the corresponding gastrocnemius muscle. A heavy spring isometric type lever was firmly attached to the freed tendon of Achilles. A thread was then attached to the isometric lever and passed over a pulley to reverse the direction to a loaded heart muscle lever for kymograph recording. The right nictitating membrane was hooked with a small fish hook and by means of a thread passed over a pulley attached to a lightly loaded heart lever for recording.

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A glass enclosed Sherrington type electrode was applied to the sciatic nerve. The uncut vagus together with the sympathetic trunk was stimulated with a Harvard type electrode shielded from shorting and drying by a thin sheet of rubber. A thyrotron stimulator supplied a 100 cycles/second source. The 100 cycles/second was selected and used in all experiments although it was realized to be a high frequency of stimulation for the cervical sympathetic trunk. This was done because it was believed to be desirable to stimulate both the sciatic and the autonomic nerves simultaneously from the same source. The current going to the cervical sympathetic trunk was reduced by passing it through an adjustable 300,000 ohm rheostat. In every experiment included in this report the original source voltage never exceeded 5 volts. In the control period the response of the nictitating membrane and the gastrocnemius muscle was set at a threshold by gradually increasing the voltage until a satisfactory recordable contraction resulted. Increasing the voltage further increased the size of the responses in each instance. The threshold which was selected was thus not the strictly subliminal one but at least there was assurance that it was well below maximum levels. Nevertheless, each experiment was not considered satisfactory unless stimulation at 5 minute intervals for 30 minutes yielded responses which were identical during the control period. Experiments were made in which each individual stimulation lasted from 0.1 second to 10 seconds. After many trials it was found that a 10 second period of stimulation was the most satisfactory one in our hands. This, of course, gave a long period of tetany of the gastrocnemius muscle which was useful because the appearance of fatigue could be easily noted. At the same time the long stimulus was ideal for causing a sustained contraction of the nictitating membrane and in addition resulted in most animals in a reflex vagal cardiac slowing. Accordingly the experiments reported here are all with a 10 second stimulation period. In interpreting the results the control responses were considered as 100 per cent. A decrease to one-half the original height, peak to baseline, was considered to be a 50 per cent reduction, etc.

In most experiments to avoid anoxia as neuromuscular block occurred the animals were given artificial ventilation. In some experiments where the effect of the drug on respiration was to be observed, no artificial ventilation was supplied and the respiratory movements were recorded by means of a chest pneumograph. All test drugs were injected rapidly into a femoral vein cannula. The dilution of each dose was calculated so that the injected volume was less than one milliliter.

RESULTS

Neuromuscular and Ganglionic Block.—As shown in tables 1 and 2, doses of 10 to 100 mg./kg. intravenously of thiamine hydrochloride produced various degrees of blocks in dogs and cats. The dose to cause complete block to stimulation of the sciatic nerve was 20 mg./kg.

TABLE 1
EFFECTS OF THIAMINE HYDROCHLORIDE ON NEUROMUSCULAR AND
GANGLIONIC TRANSMISSION IN 12 DOGS

Intra- venous Dose (mg./ kg.)	Number of Animals	Number Times Tested	Respiratory Paralysis		Sciatic-Gastro- cnemius Block		Sympathetic Trunk-Nictitating Membrane Block		Mean Blood Pressure Fall		Vagus Block	
			Degree	Duration (min- utes)	Degree	Duration (min- utes)	Degree	Duration (min- utes)	Mm./ Hg.	Duration (min- utes)	Degree	Duration (min- utes)
10	2	3	0		slight		0		0		0	
50	4	8	30 per cent	8	50 per cent	10-15	30 per cent	4-7	30	4-7	30 per cent	10-15
80	4	4	com- plete	15	com- plete	15-20	75 per cent	7-10	50-80	7-10	com- plete	20
100	2	2	com- plete	80	com- plete	48	com- plete	25	90	20	com- plete	80

in cats whereas 80 mg./kg. was necessary in the dog. Both species demonstrated ganglionic block simultaneously with the neuromuscular block. However, this was not a complete block except for the largest doses as noted in tables 1 and 2. It was also found that the duration of the ganglionic block was much shorter than that of the neuromuscular block. A typical experiment is shown in figure 1.

Respiratory Paralysis.—Five unanesthetized rabbits were given intravenous doses of thiamine hydrochloride ranging from 10 to 80 mg./kg. With doses of more than 50 mg./kg. head drop and transient apnea occurred. One rabbit died with the 80 mg./kg. dose.

In anesthetized dogs, doses of 50 to 100 mg./kg. intravenously caused apnea of variable degree dependent on the dose as shown in table 1. The apnea was complete only with doses of 80 mg./kg. or more. With this dose (80 mg./kg.), spontaneous respiratory movements were incapable of supporting the animal for the tidal volume was negligible. Artificial respiration was instituted. At 5 minute intervals the animal

TABLE 2
EFFECTS OF THIAMINE HYDROCHLORIDE ON NEUROMUSCULAR AND
GANGLIONIC TRANSMISSION IN 10 CATS

Dose (mg./kg.)	Number of Animals	Number of Times Tested	Sciatic-Gastrocnemius Block		Sympathetic Trunk-Nictitating Membrane Block	
			Degree	Duration (minutes)	Degree	Duration (minutes)
10	4	5	60-75 per cent	5-10	10 per cent	2-4
20	4	7	complete	10-16	50 per cent	4-8
50	2	3	complete	12-18	50-70 per cent	5-10

was allowed to breathe on his own to determine if the tidal volume was sufficient to maintain life. Generally at this dose level it took 15 minutes before spontaneous respiration was adequate. In each instance the degree of apnea corresponded to the degree of neuromuscular block observed simultaneously on the record of the gastrocnemius contractions on the sciatic nerve stimulation.

In anesthetized cats much the same observations were made as for the dogs except that the dose required for complete apnea was 30 mg./kg.

Blood Pressure Fall.—In each animal there was an immediate fall in the arterial blood pressure on the intravenous injection of thiamine. The degree of fall was related to the dose and the amount of ganglionic

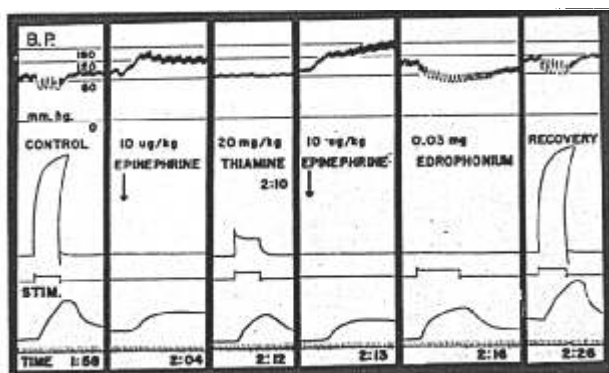


FIG. 1. Cat 14. From above down, blood pressure, gastrocnemius muscle, nictitating membrane, stimulus signal and time base in seconds. Control, left, at 1:58. Note that with stimulation there was marked vagal cardiac slowing. There was a sustained tetany of the gastrocnemius with no evidence of fatigue. The nictitating membrane showed a well developed contraction. At 2:04 a test dose of epinephrine caused a characteristically slow prolonged contraction of the nictitating membrane. The blood pressure curve showed a typical immediate rise followed by a gradually descending slope. At 2:10, 20 mg./kg. of thiamine was given intravenously. The record was taken at 2:12 during the 10 second stimulation period. Note that there had been a fall in basal blood pressure to 60 mm. of mercury and that there was little vagal cardiac slowing. The gastrocnemius tetany had diminished in amplitude to 30 per cent of its former level and shows fatigue. The nictitating membrane had 70 per cent of its control peak contraction. At 2:13 a dose of epinephrine after the administration of thiamine caused a similar rise as in the control period except that the curve continued to rise after the first peak effect showed loss of inhibitor vascular reflexes. The nictitating membrane contracted as previously so that the thiamine block was probably located in the superior cervical ganglion. At 2:14, 0.03 mg. of edrophonium was given intravenously and at 2:16 a record of the stimulation is shown. No antagonism of the neuromuscular block occurred but the vagal slowing was enhanced and the character of the nictitating membrane contraction was altered by the edrophonium. At 2:26 recovery was complete with return of vagal slowing, nictitating membrane and gastrocnemius contractions are similar to the controls. (The shift of the base line of the nictitating membrane curve is an artefact.)

block obtained as shown by the failure of the nictitating membrane to contract on sympathetic trunk stimulation (table 1). The duration of blood pressure fall also coincided with the duration of ganglionic block. Epinephrine was still capable of raising the blood pressure during the maximum action of thiamine. However, after the first peak rise the blood pressure continued to rise instead of beginning to gradually fall as in the epinephrine effect before thiamine (figure 1). Presumably this was the result of ganglionic block and hence the loss of inhibitory vascular reflexes.

Vagus Block.—In each experiment it was also found that after thiamine the slowing of the heart observed on stimulation of the vagus nerve in the neck was blocked (table 1, figure 1). In general the degree

TABLE 3
EFFECTS OF ACETYLTHIAMINE, OXYTHIAMINE AND PYRITHIAMINE ON
NEUROMUSCULAR AND GANGLIONIC TRANSMISSION IN CATS

Drug Intravenous Dose (mg./kg.)	Number of Cats	Sciatic-gastrocnemius Block		Sympathetic Trunk-Nictitating Membrane Block	
		Degree	Duration (minutes)	Degree	Duration (minutes)
Oxythiamine					
2	1	0		0	
10	4	10 per cent	8-15	0	5-8
30	3	complete		50 per cent	
Acetylthiamine					
10	4	30 per cent	10-15	slight	5-8
20	2	complete		50 per cent	
Pyrrithiamine					
1	1	10 per cent		0	
2.5	1	complete	10-15	30 per cent	5-10
3	2	complete		50 per cent	

of vagus block corresponded to the degree of nictitating membrane block. Additional experiments with hexamethonium as a ganglionic blocking agent produced an analogous result in the same animals. It could, therefore, be presumed that the vagus blocking effect of thiamine was the result of ganglionic block.

Relative Potency of Thiamine.—In order to obtain a comparative basis of the potency of thiamine, an assay was made using 3 additional anesthetized cats prepared as in the previous experiments. A dose of 20 mg./kg. of thiamine hydrochloride was the standard test dose and its effects were compared to gradually increasing doses of hexamethonium and succinylcholine. Accordingly, it was found that 0.1 mg./kg. intravenously, of succinylcholine produced a neuromuscular block and 0.25 mg./kg., intravenously, of hexamethonium produced a ganglionic block equivalent in magnitude and duration to the test dose of thiamine.

Antagonism to Thiamine.—The administration of edrophonium in doses ranging from 0.03 to 2 mg., intravenously, did not significantly alter the response to the thiamine neuromuscular block from control levels. Likewise, prostigmine in doses of 0.1 to 0.5 mg., intravenously, had no effect. If the antagonists were given when the animal had begun to emerge from the effects of thiamine, there was acceleration of the recovery but even this effect was not marked.

Effects of Acetylthiamine, Oxythiamine and Pyrithiamine.—As shown in table 3, the effects of acetylthiamine were very similar to those of thiamine. Oxythiamine and pyrithiamine also had neuromuscular and ganglionic blocking actions. However, pyrithiamine was effective in a dose of only 3 mg./kg. in contrast to oxythiamine which required a dose of 30 mg./kg. to achieve comparable blocking effects.

In other experiments, pyrithiamine and oxythiamine were administered immediately after and at intervals after an effective dose of thiamine. In no instance was antagonism observed. The administration of the metabolic antagonists produced only additive effects on the pharmacologic blocking action of thiamine.

DISCUSSION

It is important to realize that a substance used for its nutritional and metabolic actions may also have pharmacological effects especially if administered parenterally and in large doses. Chemically, thiamine belongs to a group of complex quaternary nitrogen compounds which have effects on neuromuscular and ganglionic transmission (9). Obviously it is the thiazolium portion of the thiamine molecule containing a quaternary nitrogen which is active pharmacologically. That the vitamin and cofactor activity of thiamine have little to do with the ganglionic and neuromuscular blocking activity is nicely demonstrated by the fact that pyrithiamine an antithiamine with no vitamin activity is about ten times more potent than thiamine in this respect. Oxythiamine, another antihistamine substance, further strengthens this viewpoint.

The numerous, although scattered, report of the human and animal toxicity of thiamine on parenteral administration of large doses can now be better understood (1, 2, 3). The respiratory and skeletal muscle paralysis can be safely attributed to neuromuscular block (6, 7, 8) although an earlier report ascribed it to respiratory center paralysis (10). The vascular and cardiac collapse so often reported can in part now be attributed to ganglionic blockade (5). In an earlier study the cardiovascular toxicity of thiamine was considered to be central in origin, but these results now appear to be more adequately explained by ganglionic blockade (11). A central cardiovascular depressor action for quaternary compounds has been described which has not been studied by us for thiamine (12). However, the exact coincidence of the degree and duration of the ganglionic blockade with the changes in

blood pressure in our experiments support the view that the vascular changes we observed could largely be attributed to this effect. The possibility of anaphylactoid reactions as observed in humans could not be excluded as a mechanism in this type of experiment.

Our results shed some light on a curious toxicity of the antimetabolites, oxythiamine, and pyriethamine. When these are administered to mice in an attempt to block thiamine metabolism, pyriethamine causes prompt pharmacologic effects consisting of loss of neuromuscular control. In contrast, oxythiamine does not produce this immediate syndrome but does, in time, cause the symptoms of thiamine deficiency (13, 14). Various reasons have been ascribed to this phenomenon, but it now would appear reasonable to assume that pyriethamine is causing the syndrome of neuromuscular block. This is because, as shown in our studies, it is comparatively a potent neuromuscular blocking agent and even the small doses used in antimetabolite experiments should be capable of this effect apart from the antimetabolic action. Oxythiamine being a far weaker neuromuscular blocking agent could be expected to show only the late antimetabolic effects.

Our inability to show good antagonism to the thiamine neuromuscular block by edrophonium and prostigmine is at variance with the results of others (4). This may in part be due to the different techniques employed. However, an earlier investigation also failed to show antagonism by prostigmine (15).

It would be of great interest to observe in human anesthesia if patients undergoing surgical procedures who have been receiving large doses of thiamine have unusual sensitivity to curare-like agents. In the same vein, difficulty of the maintenance of blood pressure during anesthesia in some patients may perhaps be caused by the ganglionic blocking action of thiamine.

SUMMARY

Thiamine hydrochloride in doses of 20 mg./kg. in cats and 80 mg./kg. intravenously in dogs causes complete neuromuscular paralysis. At this dose level a 50 to 95 per cent ganglionic block also exists as tested by the blood pressure fall and decrease in nictitating membrane response. After a single dose the neuromuscular block lasts on the average from 15 to 20 minutes and the ganglionic block 5 to 10 minutes. Pyriethamine is 10 times more active and oxythiamine weaker by one-third as compared to thiamine. Acetylthiamine is equal to thiamine in potency. It is important to keep in mind that metabolic agents may have significant pharmacologic actions in addition to their biochemical effects.

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