

The Potentiation of Neuromuscular Blocking Agents by Quinidine

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The interaction between quinidine and neuromuscular blocking agents was investigated in the cat anterior tibialis and the rat phrenic nerve-diaphragm preparations. The neuromuscular blockade produced by *d*-tubocurarine, succinylcholine, decamethonium and gallamine was approximately doubled in intensity and duration after quinidine. This indicates a definite interaction between quinidine and both the non-depolarizing and depolarizing muscle relaxants in producing neuromuscular blockade. Edrophonium was not effective in antagonizing a non-depolarizing blockade after administration of quinidine. Post-tetanic facilitation was less marked after a combination of gallamine and quinidine than after gallamine alone. The physician who uses the quinidine-muscle relaxant combination should be aware that an increased and prolonged neuromuscular blockade might occur.

QUININE has long been known to have neuromuscular blocking properties.¹⁻³ Recently, quinidine, the *d*-stereoisomer of quinine, has been reported to interact with muscle relaxants to produce prolonged neuromuscular blockade.⁴⁻⁷ One such case of potentiation of neuromuscular blockade by quinidine has occurred in this institution.⁸ Several mechanisms have been proposed: a weak curare-like effect,^{9,10} cholinesterase inhibition,^{11,12} and direct muscle membrane depression.⁹

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This work was presented in part at the 50th Annual Meeting of the Federation of American Societies for Experimental Biology, Atlantic City, New Jersey, April 11-16, 1966, and the 20th Annual New York Postgraduate Assembly in Anesthesiology, New York City, December 12-14, 1966. Accepted for publication June 21, 1967.

This work was supported in part by USPHS Grant 2 T01 GM 00063-09.

The following study attempts to define more precisely the characteristics of the interaction between quinidine and the clinically used muscle relaxants.

Methods

Cats, 2 to 3 kg. in weight, were anesthetized with chloralose, 60 mg./kg., and urethane, 250 mg./kg. intraperitoneally. The tendon of the anterior tibialis muscle was freed, sectioned near its point of attachment, and attached to a Grass FT.03 force displacement transducer. Muscle contractions were continuously recorded on the polygraph as discrete twitches such that twitch height was proportional to isometric contractile force. After section of the sciatic nerve high in the thigh, the peroneal nerve was isolated and shielded platinum electrodes were used for indirect stimulation of the muscle. Supramaximal stimuli (1.1 to 2.8 volts) were applied from a Grass stimulator (Model S4C). The rate of stimulation was 0.1 cps with a duration of 0.3 msec. Tetanus was administered at 40 cps for 3 sec. The sensitivity of the recording system was adjusted so that control twitch height was a minimum of 15 mm. and a maximum of 40 mm.

Five experiments were done with each muscle relaxant-quinidine sequence. Each animal served as its own control using that dose which produced a 20 to 50 per cent depression of twitch height. The muscle relaxants studied were *d*-tubocurarine chloride (*d*TC), 0.2 to 0.3 mg./kg., succinylcholine (Sch), 0.008 to 0.030 mg./kg., gallamine triethiodide, 0.8 to 1.0 mg./kg., and decamethonium bromide (ClO), 0.1 to 0.015 mg./kg. All injections were made into the jugular vein. Each animal received one relaxant and was used for only one experiment. The control dose

was repeated at least once to check for reproducibility of the preparation. One hour later, quinidine gluconate, 5 mg./kg., was then administered. Then the control dose of muscle relaxant was repeated every 45 minutes until return to the control level of depression of twitch tension occurred. At this time, the quinidine effect was no longer considered to be present.

Neuromuscular blockade was expressed as percentage of control twitch height. The duration of neuromuscular blockade was defined as that time in minutes between the injection of the muscle relaxant and return of twitch tension to 75 per cent of control height (relaxant control). The duration of quinidine effect was defined as that time between the administration of quinidine and the return to the control level of depression of twitch tension for a given dose of muscle relaxant. Post-tetanic facilitation was considered present if the first twitch following a tetanic stimulus was two or more times greater than that immediately preceding a tetanus.¹³

The ability of edrophonium to antagonize a gallamine-quinidine neuromuscular blockade was studied in 5 cats. Edrophonium chloride, 0.01 mg./kg., was given at maximum depression of twitch tension produced by gallamine before and after quinidine.

The consistency of depression of twitch tension after repeated injections of muscle relaxants was studied in 8 cats. In 4 of them, dTC, 0.25 mg./kg., was administered every 45 minutes eight times. The degree of depression of twitch height was determined. This same procedure was done in 4 experiments with Sch, 0.02 mg./kg.

In 7 cats, 4 with dTC and 3 with Sch, 5 mg./kg. of quinidine was injected 10 minutes after twitch tension had returned to control height in an attempt to produce "recurarization" as described by Schmidt⁴ and Cuthbert.¹⁴

In all experiments ventilation via a tracheostomy was controlled by a Harvard pump sufficient to maintain arterial blood gases within normal limits. Rectal temperature was maintained between 35° and 38° C. Carotid arterial blood pressures were recorded on a Grass recorder via a Statham strain gauge.

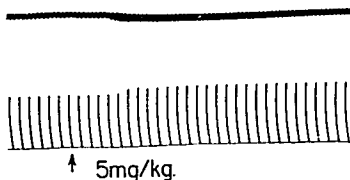


FIG. 1. When quinidine, 5 mg./kg., was given alone, no neuromuscular blockade was produced; in fact, twitch tension increased 2 to 3 mm.

The *t*-test for period observations¹⁵ was carried out for the results obtained.

The interaction of quinidine with the relaxants *in vitro* was studied in the rat phrenic nerve-diaphragm preparation described by Bulbring.¹⁶ Quinidine alone and in combination with Sch, dTC and C10 was studied. Three experiments were carried out with each neuromuscular agent. As in the *in vivo* studies, each preparation served as its own control. After determination of an appropriate dose of the muscle relaxant which produced approximately 50 per cent depression of twitch tension, quinidine sulfate was added to the bath to give a concentration of 5 µg./ml. and was maintained at that concentration in subsequent washes. The effects of the same and lower doses of the relaxant were then re-determined. Statistical analysis of these results was carried out using the Mann-Whitney Rank Order test.¹⁵

Results

In none of the *in vivo* experiments did 5 mg./kg. of quinidine given one hour after the

TABLE 1. The Effect of Quinidine on the Degree of Neuromuscular Blockade Produced by Muscle Relaxants

Drug	Mean Block Before Quinidine Percentage	Mean Block After Quinidine Percentage	Mean Potentiation Percentage
<i>d</i> -Tubocurarine*	31 ± 7.1	65 ± 10.1	34 ± 8.3
Succinylcholine*	34 ± 6.4	58 ± 9.4	24 ± 5.3
Decamethonium*	33 ± 7.8	64 ± 6.8	31 ± 6.3
Gallamine*	23 ± 4.8	58 ± 8.2	35 ± 7.6

* Five experiments were done with each muscle relaxant-quinidine sequence.

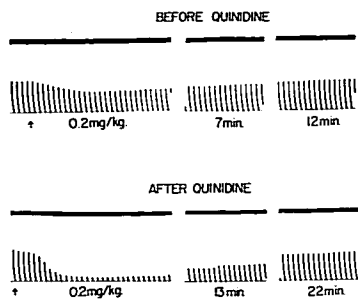


FIG. 2. The effect of quinidine on the duration and degree of neuromuscular blockade produced by *d*-tubocurarine. A 38 per cent neuromuscular blockade was produced by 0.2 mg./kg. of *d*-tubocurarine; however, after 5 mg./kg. of quinidine had been administered, this same dose of *d*-tubocurarine produced an 86 per cent neuromuscular blockade.

control dose of muscle relaxant produce a neuromuscular blockade by itself (fig. 1). In fact twitch tension usually increased 2 to 3 mm., which is consistent with prior observations.⁹

The degree of neuromuscular blockade produced by all four muscle relaxants was approximately doubled by quinidine (table 1). The mean potentiations were all highly significant statistically ($P < 0.01$). An example of quinidine potentiation of *d*TC neuromuscular blockade is depicted in figure 2, while quinidine's effect on a SCh neuromuscular blockade is demonstrated in figure 3. Comparison of these two figures further illustrates the fact that quinidine appears to potentiate both the non-depolarizing and depolarizing muscle relaxants to a comparable degree. Similar tracings were obtained with gallamine and C10 in combination with quinidine. The time to maximal depression of neuromuscular blockade was nearly the same with quinidine relaxant combination as with relaxant alone; the recovery time (return to relaxation control) after quinidine was significantly greater ($P < 0.05$) (table 2). The duration of quinidine effect was quite variable with a mean of 2.25 hours (range 1 to 5 hours).

Edrophonium's ability to antagonize a gallamine neuromuscular blockade was markedly

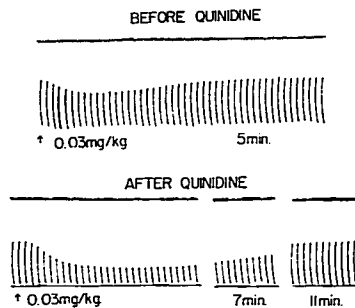


FIG. 3. The effect of quinidine on the duration and degree of neuromuscular blockade produced by succinylcholine. Succinylcholine, 0.03 mg./kg., produced a 21 per cent neuromuscular blockade. After quinidine, 5 mg./kg., had been administered, this same dose of succinylcholine produced a 63 per cent neuromuscular blockade.

reduced after quinidine. Before quinidine, edrophonium reversed 85 ± 17 per cent of the gallamine decrement in twitch tension. After quinidine, the reversal produced by edrophonium was 35 ± 10 per cent of the gallamine-quinidine decrement (table 4).

Post-tetanic facilitation was quantitated as 127 per cent increase in twitch tension during a gallamine neuromuscular blockade before quinidine. After quinidine, post-tetanic facilitation was not present.

Four cats given *d*TC every 45 minutes for 6 hours had a 38 to 42 per cent depression of twitch height. The variations in twitch height between the first and last dose were not statistically different from each other at the 5 per cent level of probability. In 4 cats given SCh every 45 minutes for 6 hours, depression in twitch heights ranged from 25 to 31 per cent between the first and last dose, and again these differences were not statistically significant.

We found the method of "recurarization" to be quite variable. In two of the *d*TC and one of the SCh experiments, twitch tension was not affected by quinidine; however, in the other 4 animals quinidine caused a slight depression of twitch tension.

In the *in vitro* studies with the rat phrenic nerve-diaphragm preparation, quinidine alone

produced no decrease in twitch tension. The relaxant dose required to produce 50 per cent depression in twitch tension was markedly reduced following addition of quinidine to the system (table 3). The potentiating effect of quinidine increased between 30 and 120 minutes. There was no evidence of fatigue during the quinidine exposure as indicated by the failure of twitch height to decrease. Full recovery was observed following each exposure to a neuromuscular blocking agent.

Discussion

Quinidine was effective in potentiating the neuromuscular blockade produced by both non-depolarizing and depolarizing muscle relaxants. The time for onset of neuromuscular blockade was not affected by quinidine. In addition to potentiating the degree of paralysis, the duration of the blockade was prolonged by quinidine. The duration of quinidine effect ranged from 1 to 5 hours. This is consistent with the case report of 6 hours of neuromuscular blockade following muscle relaxant-quinidine sequence.⁵

Two observations exclude the possibility that the increased neuromuscular blockade associated with relaxant-quinidine sequence resulted from accumulation of muscle relaxant from repeated injections, or fatigue of the preparation. Repeated injections of dTC or SCh at 45 minutes intervals for 6 hours produced no statistically significant change in the depression of twitch tension. Secondly, we found that repetitive doses of muscle relaxant

demonstrated the duration and termination of quinidine potentiation. The recordings taken after the quinidine effect was terminated, demonstrated that the depression of twitch tension with the various neuromuscular blocking agents was the same as that seen before quinidine. In the rat phrenic nerve-diaphragm preparation, full recovery was observed following each exposure to a neuromuscular blocking agent and quinidine, indicating lack of fatigue in this preparation. In this same preparation, the potentiating effect of quinidine increased between 30 and 120 minutes suggesting increased uptake by the muscle or a progressive intensity at the site of action.

Schmidt, using the "recurarization" method, found that quinidine potentiates both the depolarizing and non-depolarizing type of muscle relaxants.⁴ In contrast to these results,

TABLE 3. Interaction of Quinidine and Muscle Relaxants on the Rat Phrenic Nerve-Diaphragm Preparation

Drug	Relaxant Dose Required to Produce 50 Per Cent Depression in Twitch Tension ($\mu\text{g./ml.}$)		
	Control	After Quinidine, 5 $\mu\text{g./ml.}$	
		30 minutes	120 minutes
d-Tubocurarine	1.6 (1.2-2.2)*	1.1 (0.6-1.8)	0.5† (0.3-0.8)
Succinylcholine	10.7 (7.0-15.0)	4.7 (3.0-7.0)	2.0† (1.0-3.0)
Decamethonium	40‡	18.0† (8.0-25.0)	2.7† (2.0-3.0)

* Range.

† Significantly different from control ($P < 0.05$), Mann-Whitney Rank Order Test.

‡ Highest dose used, depression less than 50 per cent.

TABLE 2. The Effect of Quinidine on the Time of Onset and Recovery from Neuromuscular Blockade

Muscle Relaxant	Mean Time in Minutes			
	Before Quinidine		After Quinidine*	
	Maximum Depression	Return to Relaxant Control	Maximum Depression	Return to Relaxant Control
d-Tubocurarine*	2.9 \pm 1.0	14.8 \pm 3.5	3.6 \pm 1.2	25.6 \pm 1.1
Succinylcholine*	1.2 \pm 0.3	5.1 \pm 2.3	1.3 \pm 0.2	8.5 \pm 0.8
Gallamine*	2.2 \pm 1.0	10 \pm 1.8	2.4 \pm 1.4	15 \pm 2.0
Decamethonium*	1.6 \pm 0.7	10 \pm 2.4	1.4 \pm 0.2	18 \pm 3.9

* Five experiments were done with each muscle relaxant-quinidine sequence.

TABLE 4. The Effect of Quinidine on the Ability of Edrophonium to Reverse a Gallamine Neuromuscular Blockade

Degree of Gallamine Neuromuscular Blockade Reversed	
Edrophonium Before Quinidine*	85 \pm 17 per cent
Edrophonium After Quinidine	35 \pm 10 per cent

* Five experiments were done.

Cuthbert, using essentially the same method, demonstrated that quinidine always caused "recurarization" during recovery from SCh blockade, but was unable to demonstrate a similar effect following gallamine, a non-depolarizing relaxant.¹⁴ We found that "recurarization" was variable and possibly might be an insensitive indicator of potentiation.

Neither the weak curare-like effect nor the cholinesterase inhibition mechanism of quinidine-muscle relaxant interaction satisfactorily explains all of the results obtained in our series of experiments. The curare-like action of quinidine is probably not the main mechanism of potentiation for three reasons: (1) edrophonium was not completely effective in antagonizing the non-depolarizing neuromuscular blockade after quinidine; (2) quinidine potentiated a SCh neuromuscular blockade; (3) post-tetanic facilitation with the non-depolarizing blockers was decreased after quinidine. The *in vitro* experiments demonstrate that quinidine potentiation can occur, independently of blood pressure, blood flow, and blood, hepatic or renal enzymatic activity which might be considered to play a part in the *in vivo* preparations. Furthermore, pseudocholinesterase inhibition can be ruled out. Significant true cholinesterase inhibition in the muscle at the dose of quinidine used has not been completely ruled out but seems unlikely in view of the *in vitro* results.

We did not investigate the possibility that the site of action might be in the postsynaptic area. It may be of interest that the muscle relaxant dioxahexadecane (Prestonyl) resembles quinidine in that it potentiates both the depolarizing and non-depolarizing muscle relaxants. Linssen¹⁷ has assigned the site of action of dioxahexadecane to the post-neuromuscular junction by postulating that the cholinergic endplate has "intermediate" receptors and there are additional "effector" receptors which are located between the acetylcholine receptors on the endplate and the muscle membrane which is ultimately depolarized. This more distal "effector" receptor is the proposed site of action of dioxahexadecane. This might be a possible explanation for agents which potentiate both the depolarizing and non-depolarizing muscle relaxants.

Another factor which must be considered is that cinchona alkaloids are local anesthetics.¹⁰ Local anesthetics, such as procaine, can block neuromuscular transmission by interfering with the release of acetylcholine in response to the nerve action potential.¹⁵ The local anesthetic action of quinidine might explain in part its interaction with the neuromuscular blocking agents. Preliminary work in our laboratory suggests that lidocaine potentiates the neuromuscular blocking agents in a manner which is similar in degree and character to that produced by quinidine.

Summary

Quinidine potentiated the neuromuscular blockade produced by SCh, C10, dTC and gallamine in the cat *in vivo*, and in the rat phrenic nerve-diaphragm *in vitro*. Edropronium was not effective in antagonizing a non-depolarizing blockade after quinidine. No single classical mechanism can explain all these interactions. Physicians who use these drugs together should be aware that an increased and prolonged neuromuscular blockade may occur.

We are grateful to C. Philip Larson, Jr., M.D., for his helpful suggestions and criticism and to Charles F. Lee for his technical assistance.

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Surgery

HALOTHANE AND LIVER DAMAGE Numerous factors may be responsible for postoperative liver damage with or without halothane as the anesthetic agent: (1) surgical trauma to the biliary or vascular system of the liver, (2) prolonged anesthesia, (3) prolonged hypotension or shock with secondary ischemia of the liver, (4) hepatotoxic medication (antibiotics, tranquilizers), (5) infections, particularly peritonitis, (6) incubation stage of coincidental virus hepatitis, and (7) hypersensitivity reaction to halothane. Autopsy reports of 219 surgical patients over a 2-year period were studied, of these, 160 had received halothane and 59 some other form of anesthesia. In 38 patients, liver damage of varying degree was encountered. Of these 38 patients, 27 had been anesthetized with halothane, 6 of them more than once. Duration of anesthesia or the number of repeat exposures to halothane seemed to be unrelated to the degree of hepatic damage. On the other hand, associated infection (peritonitis, intra-abdominal abscesses, pancreatitis and/or cholecystitis) and prolonged circulatory collapse contributed significantly to the incidence and degree of liver pathology. In the group with severe liver damage (12 cases), there were 4 patients with acute hepatic necrosis of "unexplained" etiology. All 4 had received halothane. Two of the patients had previous exposures to halothane, 7 and 15 days earlier. Death occurred on day 4, 4, 5, and 12, respectively. Two patients who had received no halothane and died in acute liver failure showed autopsy findings which were undistinguishable from "halothane induced" hepatic necrosis. Although proof to incriminate halothane does not exist, but a causative relationship between halothane and liver damage cannot be excluded with certainty. (Jensen, H. H., and others: *Acute Postoperative Liver Damage with Special Reference to Halothane*, *Langenbeck Arch. Klin. Chir.* 317: 96 (March) 1967.) **ABSTRACTOR'S NOTE:** The most valuable aspect of this paper is the large bibliography reviewing the typical, but by no means specific findings of liver damage after exposure to halothane. The authors stress the entity of "halothane sensitization" after multiple exposures, but do not ascribe enough significance to factors responsible for ischemia of the liver, particularly iatrogenic, such as infusions of norepinephrine. Two of the "unexplained" cases could be explained on this basis. One, after an intraoperative cardiac arrest secondary to blood loss of 6,000 ml., received norepinephrine for over 36 hours and the other patient was markedly anemic before surgery. The other two "unexplained" cases had more than one exposure to halothane within two weeks.