The Effect of Alkalosis on the Action of the Neuromuscular Blocking Agents

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HYPERVENTILATION sufficient to produce alkalosis is a common practice during anesthesia. Clinical studies [1, *] have suggested that changes in acid-base balance modify the action of the neuromuscular blocking agents. Laboratory studies of this phenomenon have produced conflicting results.[2–6] This study was undertaken to obtain additional information on the effect of alkalosis on the action of *d*-tubocurarine, dimethyl tubocurarine, gallamine, succinylcholine, and decamethonium in the cat.

Methods and Materials

Twenty-two cats, each weighing 2 to 4 kg., were studied. The animals were anesthetized with 36 mg./kg. pentobarbital sodium administered intraperitoneally. The peroneal nerve was separated from the sciatic trunk and ligated at mid-thigh level. A shielded Palmer bipolar electrode was applied to its peripheral end. At five or ten-second intervals supramaximal electric stimuli consisting of rectangular pulses of 0.1-msec. duration and five to ten volt intensity were delivered to the nerve by a Grass stimulator (model S4C) via a stimulus isolation unit. The resulting twitch response of the tibialis muscle was measured with a Grass force displacement transducer (model FT-03 loaded with 300-g. springs). Arterial pressure was measured with a Statham transducer (P23A) from the contralateral femoral artery. An accordion-type pneumograph placed around the lower thorax registered respiratory movements. Ventilation was measured in some experiments by means of a Wedge spirometer (Med-Science Electronics, St. Louis). All measurements were recorded on a Grass model 5 polygraph. When necessary artificial ventilation was provided with a Palmer Ideal pump.

All drugs were injected intravenously through an indwelling catheter in a femoral vein. Sodium carbonate, 0.75–1.0 mEq./kg., was administered in an 0.8 *M* solution to produce alkalosis. Arterial *p*H and P_{CO_2} were measured by the technique of Astrup.[7] When more than one neuromuscular blocking agent was tested in the same animal, an interval of at least one hour was provided between the paired injections. Only one type of agent (depolarizer or nondepolarizer) was studied in the same animal. The sequence of testing of the agents was varied from animal to animal.

Results

In five animals the infusion of 0.75–1 mEq./kg. of sodium carbonate in ten to twenty seconds produced a transient (one–three minutes) fall in mean arterial pressure of 25–50 mm. of mercury (average, 35 mm. of mercury) and apnea of one–two minutes duration. Arterial *p*H rose 0.2–.48 unit (average, .36) and P_{CO_2} fell 2–12 mm. of mercury (average, 7 mm.). The tibialis twitch response to peroneal nerve stimulation did not change significantly (fig. 1).

The same dose of sodium carbonate was administered during the steady state or recovery phase of neuromuscular block produced by *d*-tubocurarine (100–400 μg./kg.), dimethyl tubocurarine (10–30 μg./kg.), gallamine (660–2,000 μg./kg.), succinylcholine (30–100 μg./kg.), or decamethonium (10–30 μg./kg.). The effects on arterial pressure, *p*H, P_{CO_2}, and respiration were similar to those observed in the five control experiments. In six animals, following *d*-tubocurarine, sodium carbonate antagonized the neuromuscular block by increasing the twitch response (fig. 2*A*). In

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seven of nine animals the infusion of sodium carbonate following dimethyl tubocurarine potentiated the neuromuscular block by decreasing the twitch response (fig. 2*B*). Of the remaining two animals antagonism was observed in one while in the other the block appeared to be antagonized within the first twenty seconds, but was then potentiated. The neuromuscular block produced by gallamine was also potentiated by sodium carbonate (fig. 2*C*) in five of six animals. Sodium carbonate did not affect the block in the sixth animal.

The block produced by succinylcholine was potentiated by sodium carbonate (fig. 3*A*) in five animals. However the block produced by decamethonium was antagonized by sodium carbonate (fig. 3*B*) in six animals. These results, with those of other workers in this field, are summarized in table 1.

Discussion

The choice of agent and technique for producing acid-base changes was arrived at after

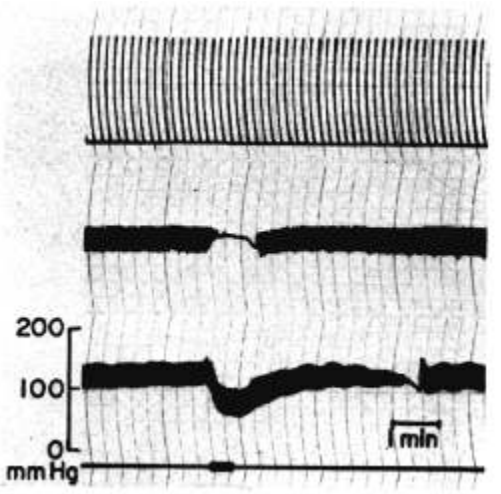

FIG. 1. Cat 4, 3.1 kg., 36 mg./kg. pentobarbibital, given intraperitoneally. Top trace, tibialis muscle twitch response to peroneal nerve stimulation; middle trace, respiratory movements; bottom trace, arterial pressure. At signal marker sodium carbonate .75 mEq./kg. intravenously. Note apnea and fall in blood pressure, but no effect on twitch response.

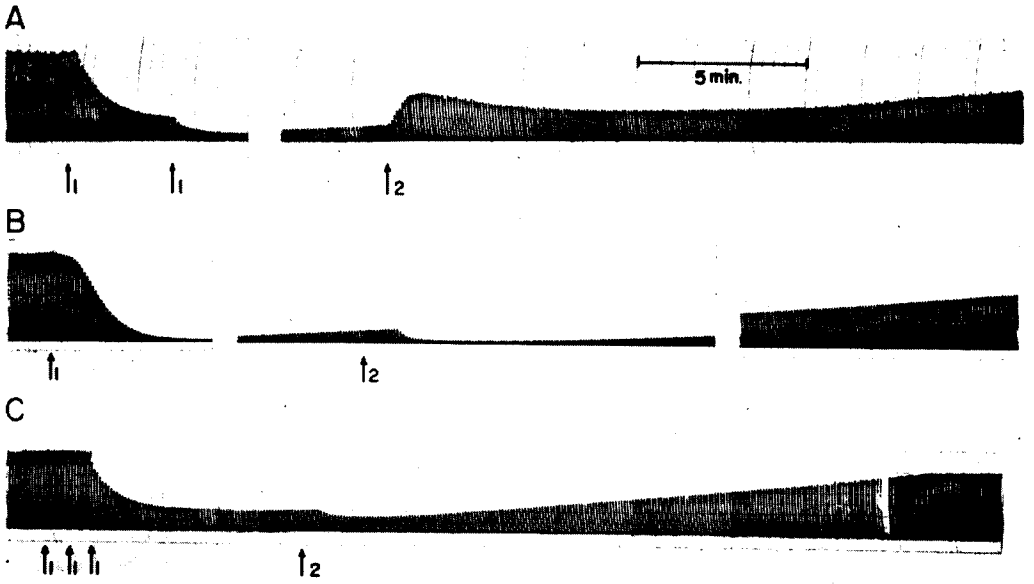

FIG. 2. Recording of tibialis muscle twitch response to peroneal nerve stimulation. (*A*) Cat 6, 2.8 kg. Pentobarbital anesthesia, 36 mg./kg., given intraperitoneally. At arrows *1*, *d*-tubocurarine 100 μg./kg. intravenously. At arrow 2, sodium carbonate 1 mEq./kg., intravenously. Time between panels is 9 minutes. (*B*) Cat 9, 2.7 kg. At arrow *1* dimethyl tubocurarine 10 μg./kg. At arrow 2, sodium carbonate 1 mEq./kg. Time between left and center panel 6 minutes, between center and right panel 11 minutes. (*C*) Cat 11, 3.2 kg. At arrows *1*, gallamine 660 μg./kg. At arrow 2 sodium carbonate .75 mEq./kg.

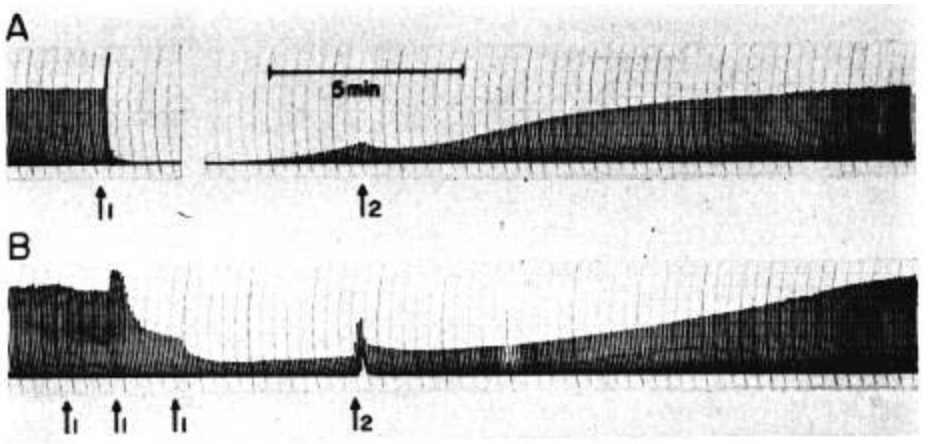

FIG. 3. Recording of tibialis muscle twitch response to peroneal nerve stimulation. (*A*) Cat 17, 2.5 kg. Pentobarbital anesthesia, 36 mg./kg., given intraperitoneally. At arrow *1* succinylcholine 80 μg./kg. intravenously. At arrow 2 sodium carbonate .75 mEq./kg. intravenously. Time between panels 11 minutes. (*B*) Cat 19, 2.6 kg. At arrows *1*, decamethonium 10 μg./kg. At arrow *2* sodium carbonate 1 mEq./kg.

preliminary experiments with hyperventilation, carbon dioxide inhalation, infusion of tris-hydroxymethyl aminomethane (THAM—an organic buffer), sodium bicarbonate, and sodium carbonate. Hyperventilation was not satisfactory because of the slow onset of alkalosis. This led to difficulty in interpretation of results especially when the neuromuscular block was waning. Carbon dioxide inhalation was abandoned for the same reason. In addition we observed, as did Payne [3] and Frederickson,[8] that carbon dioxide decreased the twitch response in the absence of the neuromuscular blocking agents. This may be due to an increase in the stimulus intensity required to evoke a maximal response and the prolongation of neuromuscular conduction time by carbon dioxide.[9]

THAM was not used because it was found to produce a neuromuscular block (Katz and Ngai, unpublished data). Sodium bicarbonate was ruled out because it decreased the muscle twitch response in the absence of neuromuscular blocking agents. Studies by Payne [5] also showed that sodium bicarbonate by itself could increase, decrease, or have no effect on the muscle twitch response to indirect stimulation. The rapid infusion of sodium carbonate was finally chosen because it produced a rapid change in *p*H and P_{CO_2} without any significant effect on twitch response in the absence of neuromuscular blocking agents.

The mechanism of action of sodium carbonate-induced alkalosis in potentiating the neuromuscular block produced by dimethyl tubocurarine, gallamine and succinylcholine, and antagonizing that of *d*-tubocurarine and decamethonium is not yet known. Some of the possibilities include *p*H-related changes in ionization of the relaxants, ionized calcium concentration, blood flow and cholinesterase activity; all of which may influence neuromuscular transmission or the neuromuscular blocking agents.[10–13] It is also possible that the action of sodium carbonate is attributable to the neuromuscular effects of changes in sodium concentration rather than *p*H effects.[14]

Changes in ionization which may be induced by a rise or fall in *p*H are known to affect the activity of many compounds.[10] Kalow,[2] Payne,[4] and Gamstorp and Vinnars [6] explained the differences in activity of *d*-tubocurarine induced by acidosis or alkalosis in terms of changes in ionization. The quaternary ammonium ions of *d*-tubocurarine exist in the completely ionized state and are not affected by *p*H changes. However, the degree of ionization of the two hydroxyl groups which have pK_a's of 8.1 and 9.1 respectively [2] may be modified by *p*H changes. Kalow [2] altered the *p*H from 6.7 to 8.7 and found that the activity of *d*-tubocurarine was inversely related to *p*H. Since the degree of ionization of the hydroxyl groups would be modified by *p*H

TABLE 1. Effect of Acidosis and Alkalosis on the Action of the Neuromuscular Blocking Agents

Agent and Investigator (s)	Preparation	Acidosis		Alkalosis	
		Respiratory	Metabolic*	Respiratory	Metabolic*
d-Tubocurarine					
Kalow[2]	Frog rectus	Potentiation	Potentiation	Antagonism	Antagonism
Payne[3,4,5]	Cat, sciatic-tibialis	Potentiation	Antagonism		Potentiation
Gamstorp and Vinnars[6]	Rabbit, sciatic-gastrocnemius		Potentiation		Antagonism
Katz, Ngai and Papper	Cat, peroneal-tibialis				Antagonism
Dimethyl tubocurarine					
Kalow[2]	Frog rectus	Antagonism	No effect	No effect	No effect
Payne[3,4,5]	Cat, sciatic-tibialis	No effect	Antagonism		Potentiation
Gamstorp and Vinnars[6]	Rabbit, sciatic-gastrocnemius		No effect		No effect
Katz, Ngai and Papper	Cat, peroneal-tibialis				Potentiation
Gallamine					
Payne[3]	Cat, sciatic-tibialis	Antagonism			Potentiation
Katz, Ngai and Papper	Cat, peroneal-tibialis				
Succinylcholine					
Payne[3]	Cat, sciatic-tibialis	Antagonism			Potentiation
Katz, Ngai and Papper	Cat, peroneal-tibialis				
Decamethonium					
Payne[3]	Cat, sciatic-tibialis	Antagonism			Antagonism
Katz, Ngai and Papper	Cat, peroneal-tibialis				

* Metabolic acidosis produced by HCl infusion. Metabolic alkalosis produced by Na_2CO_3 infusion by Gamstorp and Vinnars; Katz, Ngai and Papper. Metabolic alkalosis produced by $NaHCO_3$ by Payne. Metabolic alkalosis produced by NaOH by Kalow.

changes of this magnitude it may be reasonable to attribute his results to changes in ionization. However, the magnitude of *p*H changes in the present study (.36 *p*H unit), Payne [4] (5–20 per cent carbon dioxide inhaled, *p*H changes not stated), and Gamstorp and Vinnars [6] (mean change from normal of .3–.4 *p*H unit) would produce less than a 1 per cent change in ionization of the hydroxyl group with a pK_a of 9.1 and a maximum change of approximately 10 per cent in the hydroxyl group with a pK_a of 8.1.[10] It is, therefore, unlikely that the results of Payne,[4] Gamstorp and Vinnars,[6] or the present study are attributable to changes in ionization. Furthermore, since dimethyl tubocurarine, gallamine, succinylcholine and decamethonium do not possess ionizable groups other than the quaternary ammonium groups (which are fully ionized), modification of the activity of these relaxants could not be attributable to changes in ionization.

If changes in sodium concentration or alkalosis-induced changes in ionized calcium concentration, blood flow, or cholinesterase activity were responsible for the results observed in our experiments, it would necessitate that the neuromuscular block produced by all of the relaxants either react in a similar fashion or that each class of relaxant (depolarizer or nondepolarizer) act consistently. However, potentiation and antagonism were observed with the nondepolarizers as well as the depolarizers.

In table 1, the results of this and previous investigations are compared. It may be seen that the reported effects of *p*H changes on *d*-tubocurarine and dimethyl tubocurarine are not consistent. These inconsistencies may be attributable to species differences, different techniques of measuring neuromuscular transmission, differences in the neuromuscular preparation, and the use of different agents and dosage to produce acidosis and alkalosis. Comparison of results with gallamine, succinylcholine, and decamethonium is difficult since Payne [5] studied respiratory acidosis while we studied metabolic alkalosis. It is surprising however that with gallamine and succinylcholine acidosis and alkalosis had opposite effects, but with decamethonium the same effect (antagonism) was observed.

It would seem that further work is indicated to reconcile the results obtained by different investigators and to determine the mechanism of action of *p*H on neuromuscular transmission and the neuromuscular blocking agents.

Conclusions and Summary

The effect of sodium carbonate-induced alkalosis on the action of the neuromuscular blocking agents was studied in the cat sciatic nerve-tibialis muscle preparation. Alkalosis antagonized the action of *d*-tubocurarine and decamethonium but potentiated the action of gallamine, dimethyl tubocurarine, and succinylcholine.

The lack of agreement as to results and understanding of the mechanism of action of alterations in acid-base balance was underscored.

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INTRACRANIAL PRESSURE In candidates for neurosurgical procedures, increased intracranial pressure makes the brain more sensitive to hypoxia. If hypoxia is permitted to occur, further brain swelling will result almost at once, rendering the technical aspects of the operation more difficult. Increased intracranial pressure also makes the brain-stem centers influencing respiration and circulatory reflexes more sensitive. This may result in physiological disturbances which can affect the patient adversely under the stress of operation. Great care must be taken during the induction of anesthesia to avoid hypoxia, and this caution must be maintained throughout the surgical procedure. (*Hawkes, C. D., and Hawkes, J. M.: Preparation of the Poor Risk Patient for Neurosurgical Procedures, Western J. Surg. 70: 167 (July–Aug.) 1962.*)