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Lithium Carbonate and Neuromuscular Blocking Agents

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The effects of lithium carbonate on the responses to five neuromuscular blocking agents were evaluated in dogs anesthetized with halothane (1 per cent) and N_2O (60 per cent) in O_2. Latency (time from first twitch-height depression to maximal blockade), maximal twitch-height depression, and times to return to 50 per cent and 100 per cent control twitch tension were measured before and after intravenous infusion of lithium carbonate (1 mg/kg/min for one hour) during neuromuscular blockades produced by succinylcholine, decamethonium, gallamine, *d*-tubocurarine, or pancuronium. Lithium prolonged the latencies of neuromuscular blockades produced by 0.1 mg/kg succinylcholine and 0.1 mg/kg decamethonium by 248.1 per cent and 49.0 per cent, respectively, but had no effect on latency produced by 0.02 mg/kg pancuronium. The times for return to 50 per cent of control twitch height were prolonged by 69.5, 40.0, and 120.1 per cent, respectively. Lithium had no effect on latency or duration of blockades produced by 0.15 mg/kg *d*-tubocurarine and 0.6 mg/kg gallamine, but enhanced maximal twitch-height depressions produced by 0.9 mg/kg gallamine and 0.02 mg/kg pancuronium by 22.9 and 9.9 per cent, respectively. Twitch tensions decreased 5–10 per cent over three hours in three dogs receiving lithium infusion without relaxants. Twitch tension was depressed 0–2 per cent in three dogs after five hours of anesthesia in the absence of lithium or relaxants. Lithium prolonged the time required for neostigmine to reverse neuromuscular blockade produced by pancuronium in two of three dogs from a mean of 60 seconds to 135 seconds. (Key words: Ions, lithium; Neuromuscular relaxants, lithium.)

THE EFFICACY of lithium in the treatment of manic-depressive psychosis was first shown by Cade[1] in 1949. During recent years the use of lithium has increased and broadened to include other forms of mental disorders. Recently, two case reports have described prolonged neuromuscular blockades, one following succinylcholine,[2] the other after pancuronium,[3] in patients receiving lithium therapy. The following study was undertaken to evaluate the clinical impression that lithium potentiates the action of neuromuscular blocking agents.

Methods

Healthy, unpremedicated mongrel dogs were divided into groups of three. Anesthesia was induced with intravenous (iv) administration of thiopental, the trachea intubated, the lungs mechanically ventilated to maintain Pa_{CO_2} between 30 and 35 torr, and anesthesia maintained with 1 per cent halothane in 60 per cent N_2O and O_2. The hind leg was immobilized by a "U" bolt around the femur and another above the ankle. A Grass FT-10 force-displacement transducer was connected to the hind paw by an inflexible steel wire and the twitch tension was recorded on a model 5 Grass polygraph. The peroneal nerve at the head of the fibula was stimulated by a Grass nerve stimulator at 1/sec, 1.5-msec duration, and voltage at twice threshold (50–60 volts) by needle electrodes. Each group of three animals received a sequence of three doses of one of the following neuromuscular blocking agents as a single iv injection: 1) succinylcholine, 0.03, 0.1, and 0.3 mg/kg; 2) pancuronium, 0.1, 0.02, and 0.04 mg/kg; 3) gallamine, 0.03, 0.06, and 0.09 mg/kg; 4) *d*-tubocurarine, 0.1, 0.15, and 0.2 mg/kg; 5) decamethonium, 0.05, 0.1, and 0.2 mg/kg.

After each dose the following were measured: latency (time from initial decrease in twitch tension to maximum blockade), maximal twitch-height depression, and times for return to 50 per cent and 100 per cent of control twitch tension. After return to control twitch tension, a 30-minute interval was allowed before administering the next dose. On the following day, lithium carbonate (1 mg/kg/min by Harvard infusion pump) was infused for one hour before the same protocol was followed in the same dog.

Three dogs received only lithium carbonate (1 mg/kg/min) infusion for 180 minutes, with twitch tension being recorded continuously during and for two hours after the infusion. Three additional animals received anesthesia without either lithium or relaxant for five hours during continuous measurement of twitch height.

Three other animals were given pancuronium, 0.02 mg/kg, iv, followed in 10 minutes by neostigmine, 1 mg, iv; the time from the first indication of reversal (increasing twitch tension) to total reversal (return to baseline twitch tension) was recorded. The same sequence was followed 24 hours later after the dogs had received one hour of lithium carbonate infusion.

During each study, serum lithium, sodium, and potassium were measured by an Instrumentation Laboratory flame photometer and serum osmolality was measured by a Wescor osmometer. A percutaneous arterial line was placed in the femoral

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artery of every dog, and cardiovascular variables were monitored using Warner's method of pulse-wave analysis.[4]

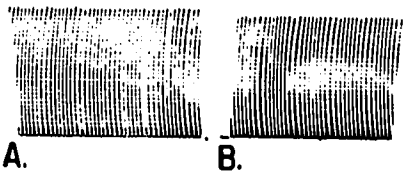
Results

Twitch heights decreased by 5–10 per cent over a three-hour period in the three dogs receiving only lithium (fig. 1), whereas 0–2 per cent decreases were observed in three dogs receiving only anesthesia for five hours.

A summary of the data is presented in table 1. Each value represents the mean from three experiments, with the range of responses for each mean value shown in parentheses. Lithium prolonged the durations of neuromuscular blockades produced by succinylcholine, decamethonium, and pancuronium but had no effect on those produced by *d*-tubocurarine and gallamine. Lithium prolonged the latencies of onset to maximal blockades for succinylcholine and decamethonium but not the others. Lithium enhanced twitch-height depressions produced by all three doses of pancuronium as well as by gallamine, 0.9 mg/kg, but it did not

TABLE 1. Neuromuscular Blocking Actions of Succinylcholine, Decamethonium, *d*-Tubocurarine, Gallamine, and Pancuronium before and after Infusion of Lithium Carbonate (Mean, N = 3, Range of Responses in Parentheses)

	Latency (Sec) Onset of Maximal Blockade		Time (Min) Return to 50 Per Cent Control		Time (Min) Return to 100 Per Cent Control		Per Cent of Control in Twitch Depression	
	Before	After	Before	After	Before	After	Before	After
Succinylcholine 0.03 mg/kg	39.3 (5–61)	86.3 (10.5–174)	6.3 (4.1–8.5)	10.1 (9–11.2)	8.6 (4.2–14.4)	15 (7.5–26)	73 (30–100)	75 (45–100)
0.1 mg/kg	27 (4–47)	94 (54–144)	14.1 (11.7–17)	23.9 (20.3–29.5)	19.8 (14.7–26.6)	59.9 (25.1–120)	97.7 (93–100)	96.7 (90–100)
0.3 mg/kg	19.3 (4–40)	108 (60–156)	16.6 (16–17.2)	31.4 (28.4–34.5)	20.3 (20–21.5)	36.6 (33.2–40)	100 (—)	95 (90–100)
Decamethonium 0.05 mg/kg	107 (98–115)	147 (129–160)	22.1 (19–23.2)	36.6 (31.2–39.9)	27.2 (25–29.1)	42.5 (38.3–44.8)	85.5 (80.0–92.0)	91 (87–93)
0.1 mg/kg	51 (35–60)	76 (66–71.5)	67.9 (66–71.5)	93.7 (89.0–95.3)	82.3 (79.3–84.1)	124.5 (118.2–127)	93 (90–98)	95 (92–98)
0.2 mg/kg	26 (13–29)	34.5 (31–42)	119.5 (112–129.5)	127 (120–135.5)	144.2 (138–146.5)	158.6 (150.5–169.5)	96 (93–98)	98 (96–100)
d-Tubocurarine 0.1 mg/kg	16 (0–28)	43 (0–110)	2.1 (0–5.5)	4 (0–5)	3.8 (0–9.5)	5.7 (0–10)	53 (0–100)	27 (0–50)
0.15 mg/kg	15 (8–22)	23 (7–40)	33 (27–46)	25 (20–28)	49 (34–76)	45 (33–63)	100 (—)	89 (80–100)
0.2 mg/kg	21 (7–39)	29 (9–40)	64 (23–80)	40 (23–50)	97 (56–160)	78 (56–119)	100 (—)	92 (82–100)
Gallamine 0.3 mg/kg	11.6 (0–27)	5.3 (0–8)	39 (0–62)	1.5 (0–2)	2.6 (0–3.9)	2.8 (0–4)	31.7 (0–60)	33.3 (0–70)
0.6 mg/kg	15.3 (6–24)	18.7 (7–29)	16.3 (14–17.5)	18 (16–22)	42.7 (36–49)	32.7 (31–35)	67.7 (64–72)	77 (70–87)
0.9 mg/kg	9 (5–12)	7.7 (7–9)	39 (33–45)	45.7 (40–57)	62.3 (60–66)	64.5 (62–66.5)	70 (67–72)	86 (75–100)
Pancuronium 0.01 mg/kg	56 (49–69)	50 (49–52)	9.9 (8.7–10.2)	20.2 (18.1–22.7)	16.5 (14.2–17.4)	26.7 (22.1–28)	73 (68–75)	99.3 (98–100)
0.02 mg/kg	42 (35–60)	68 (49–78)	18.2 (16.1–21.1)	41.7 (38.3–43.8)	26.4 (24.4–28.2)	60.5 (57–62.3)	91 (86–94)	100 (—)
0.04 mg/kg	23 (19–27)	20 (18–24)	39.9 (36.1–42)	68.4 (64–71.5)	58.4 (54.9–61.2)	95.6 (91.2–98.5)	93 (91–97)	100 (—)



A. Control twitch tenson
B. Twitch tension after 3 hours of Lithium 1mg/kg/min infusion.

FIG. 1. Effect of lithium on twitch tension.

potentiate the twitch-height depressions produced by succinylcholine, decamethonium, and *d*-tubocurarine.

Serum lithium levels were 0.10 ± 0.004 mEq/l (mean ± SE, n = 10) before the infusion of lithium carbonate, 3.0 ± 0.1 mEq/l after 60 minutes of infusion, and 1.6 ± 0.05 mEq/l 120 minutes after the completion of lithium infusion. Serum sodium and potassium levels, 142.0 ± 4.5 mEq/l and 4.6 ± 0.006 mEq/l during the control periods, respectively, remained unchanged during the experiment. Serum osmolality was 300.0 ± 5.5 mOsm/l during the control period and also was not changed during the study.

Lithium prolonged the reversal times of pancuronium blockade by prostigmine, 1 mg, iv, in two of three dogs (fig. 2), from a mean of 60 seconds to 135 seconds.

The effect of lithium on plasma pseudocholinesterase activity was evaluated in 66 manic-depressive patients receiving chronic lithium therapy, using the t-test cholinesterase kinetic test (EM Diagnostics Catalog #3811); all had normal plasma pseudocholinesterase levels (3.8–9.1 IU/l; normal range 3.6–9.5 IU/l).

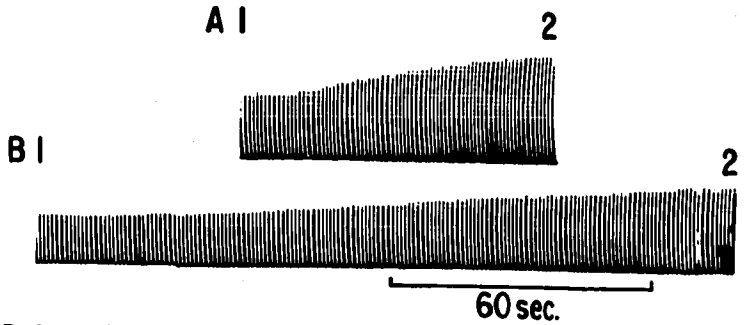
Cardiovascular variables remained stable during these studies. In contrast to findings of other investigators,[5] no persistent increase in cardiac output, mean arterial pressure, stroke volume, peripheral vascular resistance, or heart rate was observed during infusion of lithium.

Discussion

Although lithium has been reported by Brainsteanu and Volle[6] to increase neuromuscular transmitter release, others[7,8] have demonstrated inhibition of acetylcholine release. Vizi *et al.*[9] found inhibition of acetylcholine synthesis by lithium in rat-brain cortex as well as reduced acetylcholine release from nerve terminals in strips of guinea pig ileum. The slight (5–10 per cent) reduction in twitch height induced by the lithium infusion in this study could be explained by inhibition of either transmitter synthesis or transmitter release.

An additional mechanism by which lithium could produce neuromuscular blockade is a possible effect on the electrophysiology of the neuromuscular junction. The atomic radii of lithium and sodium are 1.225 and 1.575 Å, respectively.[10] This similarity in ionic sizes may explain why lithium is transported into the cell with sodium during cellular depolarization. However, lithium influx is estimated to be about 70 per cent that of sodium,[11] and lithium extrusion from the cell occurs at only 10 per cent of the rate of sodium extrusion.[12] Thus, lithium is an imperfect substitute for sodium during cellular depolarization. Furthermore, the accumulation of lithium intracellularly, because of slow extrusion from the cell, could also produce a reduction (more positive) of resting membrane potential, which in turn could reduce the height of action potentials, as well as reduce the effectiveness of the Na–K pump that requires ATPase activated by Na and K ions.[13,14] Wespi[15] has demonstrated a loss of intracellular K induced by lithium, and Onodera and Kamakawa[8] have also reported a reduced endplate potential in lithium-bathed muscle preparations.

If lithium interferes with acetylcholine synthesis



A. Before Lithium
B. After Lithium 1mg/kg/min for 1 hr. infusion
1-first indication of increasing twitch tension
2-return to control twitch tension

FIG. 2. Effect of lithium on reversal of pancuronium (0.02 mg/kg) neuromuscular blockade by 1 mg neostigmine, iv.

and/or release and exerts a depressant action on electrophysiologic phenomena, one might expect lithium to potentiate the muscle-relaxant actions of nondepolarizing as well as depolarizing neuromuscular blockers. However, in the present study, lithium potentiated the actions of pancuronium, succinylcholine, and decamethonium, but not those of *d*-tubocurarine and gallamine.

The latter observation suggests that the mechanisms of neuromuscular blockades by the three nondepolarizing agents may not be identical. Indeed, there is evidence to suggest that all three drugs, pancuronium, gallamine, and *d*-tubocurarine, have both pre- and postjunctional actions at the myoneural junction.[16–21] However, the experimental models for these studies were different, thus making direct comparisons of results difficult. In fact, differences in results may also reflect differences in drug action. Although the blocking actions of these agents can be reversed by cholinesterase inhibitors,[16] Wong and Jones[22] demonstrated a synergistic effect of *d*-tubocurarine and gallamine on the rabbit gastrocnemius preparation, suggesting different mechanisms of blockade for these two drugs. Galindo[21] has also demonstrated different pre- and post-junctional effects for pancuronium and *d*-tubocurarine, utilizing a rat phrenic nerve–diaphragm preparation.

It is difficult to explain why lithium potentiated the effect of pancuronium but not those of *d*-tubocurarine and gallamine in terms of differential effects on acetylcholine release or synthesis or pre- and postjunctional effects. One possibility, however, is that pancuronium may have a more profound effect on cellular distribution of sodium and potassium than *d*-tubocurarine or gallamine. Pancuronium has a steroid moiety as part of its massive structure[16]; the other two do not. If pancuronium has mineralocorticoid action, as many steroids have, one would expect intracellular accumulation of Na and depletion of K, electrophysiologically similar to the effect of lithium presented above. Another possibility is that pancuronium also has a depolarizing blocking action in addition to its nondepolarizing blocking action.

That lithium prolonged the reversal time of pancuronium blockade by prostigmine (fig. 2) would be compatible with the finding that lithium may inhibit synthesis or release of acetylcholine at the nerve terminal.

The potentiating effect of lithium on the durations of blockades produced by succinylcholine and decamethonium is explicable on the basis of reduced acetylcholine synthesis or release and the electrophysiologic effects of lithium. The prolongation of latency of the depolarizing agents by lithium would be compatible with the observation that lithium is less permeable than sodium,[11] therefore the rate of depolarization is delayed. Lithium had no effect on plasma pseudocholinesterase activity in 66 manic-depressive patients receiving chronic lithium therapy. Milstoc *et al.*[23] have also reported normal plasma pseudocholinesterase activity, but reduced erythrocytic cholinesterase activity, in manic-depressive patients receiving chronic lithium therapy. These clinical findings tend to suggest that pseudocholinesterase abnormality was not a mechanism of lithium-potentiated succinylcholine blockade.

The lack of change in serum sodium, potassium, and osmolarity during our canine study eliminates these variables as possible contributory causes of the alteration of responses to the neuromuscular blocking agents.

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Circulation

COLLOID ONCOTIC PRESSURE Measurements of colloid oncotic pressure (COP) (using an osmometer with a transducer membrane system), total plasma protein, and serum albumin in 35 specimens of bank blood yield values of 26.1 cm H_2O, 7.7 g/100 ml, and 4.1 g/100 ml, respectively. The mean values for 60 healthy adult volunteers were 33.8 cm H_2O for COP, 7.5 g/100 ml for total plasma protein, and 4.3 g/100 ml for serum albumin. One hundred patients undergoing operations on the abdomen, thorax and extremities involving extensive tissue dissection were divided into two equal groups. Group I received albumin in the form of purified protein fraction, 5 per cent albumin, or salt-poor albumin, in addition to whole blood and crystalloid used for fluid replacement. Group II received only whole blood and crystalloid. Preoperative values of COP were not different in the two groups. Patients in Group I received an average of 53 g of albumin during the procedure. Postoperatively they showed a small increase in COP and a significant increase in serum albumin. In Group II, postoperative measurements revealed significant decreases in COP from 25.2 to 21.5 cm H_2O, in total protein from 6.1 to 5.4 g/100 ml, and in serum albumin from 3.4 to 3.2 g/100 ml. Significant decreases in COP, total protein, and serum albumin also occurred in eight patients who received packed erythrocytes reconstituted in physiologic saline solution for fluid replacement. (*Howland WS, and others: Colloid oncotic pressure and levels of albumin and total protein during major surgical procedures. Surg Gynecol Obstet 143: 592–596, 1976.*) ABSTRACTER'S COMMENT: The authors' data show significant decreases in colloid oncotic pressure and serum albumin in patients who did not receive supplemental albumin intraoperatively. Whether an average colloid oncotic pressure of 21.5 cm H_2O or an average serum albumin of 3.2 g/100 ml is of clinical significance must be considered controversial at present [AB].