Department of Anesthesiology, University of Texas Southwestern Medical School, for constructive evaluation of this paper.

Authors' note: As of July 1975, all clinical investigation of chymopapain has ceased, except double-blind studies comparing the drug with a placebo. Because the initial data, unpublished, reveal no difference between chymopapain and placebo in effectiveness, it is anticipated that a new drug application will not be granted by the Food and Drug Administration in the near future.

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Potentiation of Succinylcholine Neuromuscular Blockade by Lithium Carbonate

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Lithium was first used by Cade[1] in the treatment of manic-depressive psychosis in 1949. Recently, its use has increased and broadened to include other psychiatric disorders.[2–4]

One previous report described a case of prolonged neuromuscular blockade with pancuronium bromide in a patient on chronic oral lithium therapy.[5] The present report describes a case of prolonged neuromuscular blockade following succinylcholine in a patient being treated by chronic oral administration of lithium. This clinical observation has been substantiated in the laboratory.

Report of a Case

A 38-year-old Caucasian woman with a history of manic-depressive psychosis was seen at 38 weeks' gestation in active labor. Serum lithium levels were reported to be 1.2 mEq/l while the patient was taking 1.5 g lithium carbonate daily, orally. Physical examination disclosed no abnormality except massive obesity (weight 320 pounds). An emergency cesarean section was performed because of fetal bradycardia. Anesthesia was induced with pancuronium bromide, 0.5 mg, thiopental, 350 mg, and succinylcholine, 150 mg, iv, followed by a succinylcholine drip (approximately 310 mg succinylcholine, total, in 120 minutes). A 5 pound, 6 ounce, female infant (Apgar scores 5 and 9) was delivered uneventfully.

Postoperatively, the patient remained apneic for

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TABLE 1. Effects of Lithium Carbonate Infusion (1 mg/kg/min) for an Hour on Latency and Duration of Succinylcholine Neuromuscular Blockade

	Before Lithium					After Lithium			
	Dose (mg/kg)	Latency*	Time (Minutes) to Return to 50 Per Cent Control	Time (Minutes) to Return to 100 Per Cent Control	Maximum Twitch Height Depression Obtained (Per Cent)	Latency*	Time (Minutes) to Return to 50 Per Cent Control	Time (Minutes) to Return to 100 Per Cent Control	Maximum Twitch Height Depression Obtained (Per Cent)
Dog 1	0.03	5 sec	8.5	14.4	100	10.5 sec	11.2	26	100
	0.1	4 sec	17	26.6	100	54 sec	29.5	>120	100
	0.3	4 sec	56	76	100	Dose not given; dog did not recover from previous dose after 2 hours			
Dog 2	0.3	61 sec	4.1	7.1	90	2.9 min	9	11.5	80
	0.1	30 sec	13.7	18.1	100	2.4 min	22	25.1	100
	0.3	14 sec	16	20	100	1 min	34.5	40	100
Dog 3	0.03	52 sec	Achieved only 30 per cent blockade	4.2	30	64 sec	Achieved only 45 per cent blockade	7.5	45
	0.1	47 sec	11.7	14.7	93	1.4 min	20.3	34.5†	90
	0.3	40 sec	17.2	21.5	100	2.6 min	28.4	33.2	90

* Time from first twitch-height depression to maximal blockade.
† Posttetanic facilitation and fade occurred.

four hours. Stimulation of the ulnar nerve with a Blockade monitor revealed possible, though not definite, signs of phase 2 block.[6] After four hours of mechanical ventilation, the patient could raise her head, spontaneous tidal volume was 450 ml, with forced vital capacity 900 ml, and hand-grip strength was good. Therefore, the trachea was extubated. Serum pseudocholinesterase level, determined on the first postoperative day, resulted in a dibucaine number of 73 (above 70 = normal homozygote).

In order further to evaluate our clinical impression of lithium potentiation of succinylcholine, the following study was done.

Methods

In six healthy, unpremedicated mongrel dogs, anesthesia was induced with thiopental (12–15 mg/kg, iv). The tracheas were intubated and the dogs mechanically ventilated to maintain Pa_{CO_2} 30–35 torr. Anesthesia was maintained with 1 per cent halothane in 60 per cent N_2O and O_2. A Grass FT-10 force-displacement transducer was connected to the left hind paw by an inflexible steel wire and twitch tension recorded on a Model 5 Grass polygraph. The peroneal nerve at the head of the fibula was stimulated by a Grass peripheral-nerve stimulator at 1/sec, 1.5 msec duration, and voltage at twice threshold (50–60 volts). To three animals, after baseline recording, succinylcholine was given in three doses, as follows: 1) 0.03 mg/kg, iv; 2) 0.1 mg/kg, iv; 3) 0.3 mg/kg.

After each dose, twitch height was allowed to return to control, followed by a 30-minute interval before the next dose. On the following day the same protocol was followed on the same dog after an hour of intravenous infusion of lithium carbonate (1 mg/kg/min by Harvard infusion pump).

Three animals received only infusion of lithium carbonate (1 mg/kg/min) for 60 minutes. Twitch tension was recorded during and two hours following lithium infusion.

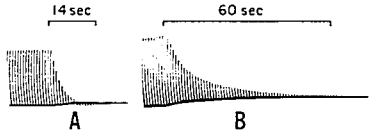

Fig. 1. Prolonged latency with lithium, Dog 2 (table 1), succinylcholine dose 0.3 mg/kg. *A*, control before lithium; *B*, after lithium.

During each study, serum lithium, sodium and potassium were measured by an Instrumentation Laboratories flame photometer and serum osmolality was measured by a Wescor osmometer. A percutaneous arterial line was placed in the femoral artery of every animal and cardiovascular values were monitored during lithium infusion by Warner's method[7] of computer analysis.

Results

Lithium potentiated the duration of succinylcholine blockade (table 1). Dog 3 manifested a phase 2 type of blockade after tetanic stimulation following 0.1 mg/kg of succinylcholine and one hour of lithium infusion (table 1). Latency (time from first twitch-height depression to maximal blockade) was also significantly prolonged following lithium administration (fig 1). Lithium carbonate infusion alone decreased twitch height by 5–10 per cent in three dogs over the three-hour period. Serum sodium, potassium and osmolality were measured (table 2), with no significant change observed in the one-hour lithium infusion or the ensuing two hours.

During the one-hour lithium infusion, there were average increases in mean arterial blood pressure of 12 per cent, stroke volume of 22

Table 2. Serum Lithium, Sodium and Potassium Concentrations and Osmolalities*

	Lithium (mEq/l)	Sodium (mEq/l)	Potassium (mEq/l)	Osmolality (mOsm/l)
Control	0.10 ± 0.04	143.3 ± 3.13	4.80 ± 0.12	305.0 ± 6.45
1.2 ±0.12 g Li over 1 hour	3.10 ± 0.11	142.0 ± 4.61	4.57 ± 0.06	304.0 ± 3.71
1 hour post-lithium	1.63 ± 0.06	142.0 ± 4.95	4.20 ± 0.18	294.0 ± 3.17
2 hours post-lithium	1.63 ± 0.06	142.0 ± 4.19	4.57 ± 0.25	295.5 ± 4.18

* Mean ± SE (n = 3).

per cent, and cardiac output of 14 per cent. No significant change was observed in peripheral vascular resistance or heart rate. These results are compatible with the findings of others.[8]

Discussion

The interaction of neuromuscular blocking agents and lithium is a relatively unexplored area. There has been only one previously published case of lithium potentiation of pancuronium blockade.[5] Brainisteanu and Volle[9] have recently reported a prejunctional effect of increasing transmitter release by lithium in the frog nerve–sartorius muscle preparation. However, in similar preparations, Kelly[10] and Onodera and Yamakawa[11] have data to suggest a reduction of transmitter release; Kelly[10] also observed an increase in the frequency of miniature endplate potential spikes (MEPP's) during failure of endplate potential (EPP) induced by lithium chloride. Vizi *et al.*[12] have shown that lithium may inhibit acetylcholine synthesis of rat-brain cortex slices and release acetylcholine from the nerve terminal of guinea-pig ileum strips.

A reduction in the synthesis and/or release of acetylcholine at the nerve terminal could certainly potentiate the neuromuscular blocking action of succinylcholine. Our data show that lithium infusion alone did produce a 5–10 per cent reduction in twitch height. That lithium also increased the latency time of onset of succinylcholine blockade may be explicable on the basis that lithium may also reduce the sensitivity of the muscle endplate to succinylcholine depolarization, thus delaying the onset of maximal neuromuscular inhibition. Serum sodium, potassium and osmolalities were not significantly changed in our animal study, which tends to eliminate alteration of these variables as a possible cause of potentiated neuromuscular blockade. We have also determined plasma cholinesterase levels of 52 patients being treated by chronic oral administration of lithium, all of whom had normal values (3.8–9.1 IU/l; normal range 3.6–9.5 IU/l).§

§ EM Diagnostics Catalog #3811, 1-test Cholinesterase Kinetic Test.

The present report suggests that lithium potentiated succinylcholine blockade in a patient and in the dog. The plasma lithium levels in dogs obtained during this study are compatible with the levels obtained in humans during oral lithium therapy[13] (table 2). These results would indicate that neuromuscular blocking agents should be used with caution in patients receiving chronic lithium treatment, particularly since the number of these patients is constantly increasing.

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