The Antiarrhythmic Effect of Lithium Chloride for Experimental Ouabain-Induced Arrhythmias[1] (37208)

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Epidemiologic studies in several countries have shown that death rates due to arteriosclerotic heart disease are inversely related to the hardness of the local water supply (1–3). This increased cardiac mortality in residents of soft water areas includes an excessive number of sudden deaths, which may be the result of an increased susceptibility to lethal arrhythmias (4). Lithium is found in high concentrations in hard water (5) and has been proposed as the etiology of the difference in cardiac mortality by providing a protective effect from lethal arrhythmias (6). This proposal is strengthened by the known effects of lithium on catecholamine metabolism (7–11). It has been reported to accelerate presynaptic destruction of norepinephrine in the brain without being released (8). Additional evidence that it may limit synaptic neurotransmitters includes evidence that in low concentration lithium inhibits electrical stimulation-induced release of norepinephrine from brain slices (10).

These metabolic effects of lithium could well affect the occurrence of catecholamine-related cardiac arrhythmias which are well documented in man (12–13).

The following animal studies were carried out to determine whether there is an antiarrhythmic effect of lithium on experimentally induced arrhythmias.

Methods. Six mongrel dogs were studied in the fasting state under pentobarbital anesthesia given in a dose of 30 mg/kg initially, with supplemental doses given as necessary during the study to maintain a moderately deep level of anesthesia. The femoral artery and vein were cannulated with polyethylene tubing under sterile conditions, and electrocardiographic monitoring was obtained using a lead which showed clear identification of the P, QRS, and T components.

Ouabain was then given intravenously according to the method of Alberti *et al.* (14) in a dose of 40 μg/kg of body weight, with supplemental doses of 100 μg given at 10 min intervals until an unequivocal and sustained arrhythmia was produced. Arterial blood samples for pH, pCO_2, pO_2, sodium and potassium were obtained before ouabain was injected, and at 10, 20, 30, 45 and 60 min, and at 30 min intervals thereafter until the arrhythmia subsided. The study was then terminated, the catheters were removed, and the incisions were closed using sterile technique.

These same animals were then restudied after an interval of at least 7 days, with each dog serving as his own control. The animal was again anesthetized and instrumented in the same manner as before. Each animal was then given the same dose of ouabain which was previously required during the initial study of that animal to produce a sustained arrhythmia; if this did not produce an arrhythmia, supplemental doses of 100 μg were given at 10 min intervals until a sustained arrhythmia was produced. Three minutes after the arrhythmia was established, an infusion of 1 *N* lithium chloride solution was started, using a Harvard infusion pump at a rate which would deliver 0.5 mEq of lithium chloride/min. This dose was selected to achieve a blood lithium level known to be safe in human subjects (15). Arterial blood

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samples for lithium, sodium, potassium, pH, pCO_2, and pO_2 were obtained before ouabain injection and at 10, 20, 30, 45, and 60 min, and then at 30 min intervals thereafter until the arrhythmia terminated. Three animals were studied a third time on a different day, so that nine sets of data on the effects of the lithium chloride infusion on the ouabain-induced arrhythmias were obtained. All animals were intubated with a cuffed endotracheal tube, and respiration was controlled with a Harvard respiration pump. Body temperature was maintained in a normal range using a water-filled circulation blanket as necessary. All animals were treated prophylactically with cephaloridine during the study and were housed and fed identically. At the termination of the study, all of the animals were sacrificed.

Sodium and potassium serum levels were determined with a flame photometer. Serum lithium levels were determined with a Perkin-Elmer atomic absorption spectrophotometer, Model 290, with a sensitivity of 0.005 ppm. Arterial pH, pCO_2, and pO_2 were determined using an Astrup blood gas analyzer. Statistical analysis of the data was performed using the t test for paired samples.

Results. A. Type of arrhythmia. The arrhythmias induced by ouabain during the control period included three animals with ventricular tachycardia, two with atrioventricular dissociation, and one with ventricular bigeminal rhythm. When these animals were rechallenged with ouabain on one or more occasions, there were six cases of ventricular tachycardia, two with ventricular bigeminal rhythm, and one with atrioventricular dissociation.

B. Duration of arrhythmia. Lithium treatment produced a significant reduction in the duration of the arrhythmias with a mean of 69 min compared to the untreated control animals in which the mean duration of the arrhythmia was 140 min, $p < 0.01$ (Table I).

C. Serum lithium level. Serum lithium levels ranged from 2.6 to 7.8 mEq/liter, with a mean level of 5.6 mEq/liter at the time of conversion of the arrhythmia. Therapeutic serum lithium levels were attained within 20 to 30 min of infusion (Fig. 1, Table II).

D. Serum sodium and potassium. There was no significant change in sodium or potassium during the control period or during the lithium infusions (Table III).

E. Acid-base balance. There were no significant fluctuations in acid-base balance, and the changes in arterial pH are shown in Table III.

F. Arterial pO_2 and pCO_2. These parameters remained within physiologic limits during the studies.

Discussion. Our study demonstrated that lithium chloride caused a significant reduction in time of offset of ouabain-induced arrhythmias. The shortening of arrhythmia duration was not accompanied by significant changes in serum sodium and potassium, arterial blood gases, or acid-base balance. The

TABLE I. Correlation of Serum Lithium Level with Offset Time of Arrhythmias for Control and Lithium-Treated Animals.

Animal no.	Control		Lithium-treated		Lithium level at end of arrhythmia (mEq/liter)
	Min	Ouabain dose (mg)	Min	Ouabain dose (mg)	
1 a[a]	201	0.71	90	0.76	7.8
b[b]			44	0.91	7.2
2	31	0.69	25	0.69	2.6
3	214	0.70	48	0.90	6.0
4	121	0.76	89	0.76	5.0
5 a	55	0.78	50	0.78	3.2
b			44	0.78	4.5
6 a	190	0.74	154	0.74	7.5
			75	0.94	6.6
Mean	140		69		

[a] Data from first study day.

[b] Data from second study day.

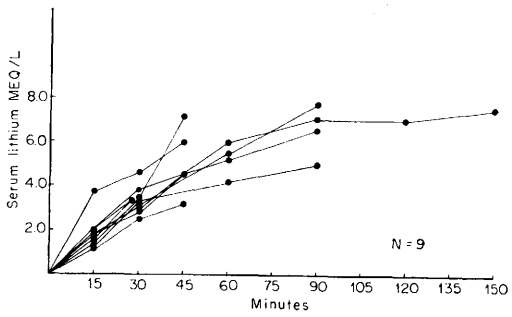

FIG. 1. The serum lithium concentration for each animal is shown on the vertical axis and minutes of infusion on the horizontal axis. Therapeutic lithium levels are achieved in 20–30 min, and there is a continuous increase in the blood level through at least the first 90 min of infusion. One animal shows a plateau in serum lithium level between 90 and 150 min.

mean serum lithium level at the time of conversion of the arrhythmia was 5.6 mEq/liter, with a range of 2.6 to 7.8 mEq/liter.

In toxic doses, lithium produces marked electrocardiographic abnormalities consisting of increased T wave amplitude, atrial and ventricular arrhythmias, QRS widening, and ST segment changes (16–18). With lower doses such as those used to treat psychiatric patients, T wave changes, usually flattening, iso-electricity, and occasional inversion have also been reported (19, 20). Some investigators have attributed the ECG changes to the hyperkalemia observed during some studies (16, 17), but others have noted ECG abnormalities with normal serum potassium levels (17, 19, 20). In contrast to these studies, we did not observe either the ECG abnormalities or serum potassium derangements with the dosage of lithium that we used. Figure 2 shows serial ECG rhythm strips of a representative dog with the corresponding serum lithium and potassium levels. There is an increase in T wave and QRS voltage and the sinus rate increased from 188 to 200 per min, but no conduction of QRS abnormalities are present.

Lithium is known to have a wide variety of physiological effects, but its mechanism of action is unknown (21). At present, there is no direct evidence that would explain how lithium may influence arrhythmias; it may act indirectly through its effects on catecholamine metabolism, as has been postulated to explain its efficacy in psychiatric disorders (6). Recent studies show that lithium has prominent effects on catecholamine metabolism in central nervous system tissue (8–11). Limitation of central neurotransmitters at the synapse in cardiac nerve tissue by lithium could possibly explain its antiarrhythmic effects which we have observed. Additional studies are required to determine whether lithium alters catecholamine metabolism in cardiac tissue as well, and thereby influences certain catecholamine-related arrhythmias (12, 13).

Another line of evidence suggesting a possible electrophysiologic basis for the effect of lithium on arrhythmias is based upon studies utilizing rabbit sinus node and canine

TABLE II. Serum Lithium Concentration.[a]

Animal no.	Control—onset of arrhythmia 0	After start of lithium infusion (min) 15	30	45	60	90	120	150
1 a[b]	0.02	1.3	3.3		5.5	7.8		
b[c]	0.007	2.0	3.5	7.2				
2	0.1	1.7	2.6					
3	0.01	2.7	4.7	6.0				
4	0.007	1.4	2.6		4.1	5.0		
5 a	0.1	1.2	2.5	3.2				
b	0.007	1.8	3.0	4.5				
6 a	0.005	1.8	3.6		6.0	7.1	7.0	7.5
b	0.002	2.0	3.8		5.3	6.6		

[a] Lithium concentration in table expressed in millequivalents per liter.
[b] Represents first study day.
[c] Represents second study day.

TABLE III. Mean Serum Sodium, Potassium and Arterial pH.

	Basal		20 min		End of arrhythmia	
	Control	Lithium	Control	Lithium	Control	Lithium
Mean serum sodium	145	149	144	148	143	143
Standard error	1.5	2.1	1.7	2.7	2.2	1.6
Mean serum potassium	3.8	3.6	3.8	3.8	4.4	4.3
Standard error	0.1	0.1	0.2	0.1	0.2	0.3
Mean arterial pH	7.39	7.45	7.41	7.46	7.29	7.33
Standard error	0.02	0.04	0.01	0.02	0.04	0.02

Purkinje fibers, in which lithium chloride prolonged diastolic depolarization and depressed the rate effects of epinephrine; also, paced Purkinje fibers demonstrated a reduction in resting potential, overshoot, and *dv/dt*, while conduction time, action potential duration, and effective refractory period were prolonged (22). However, we did not observe any abnormalities in either atrioventricular or intraventricular conduction, and the sinus rate increased rather than decreased during the lithium infusions.

In the experimental model used in our study, lithium chloride shortened the duration of ouabain-induced arrhythmias, but additional studies are necessary to determine whether this is due to a general antiarrhythmic action or possibly a more specific effect

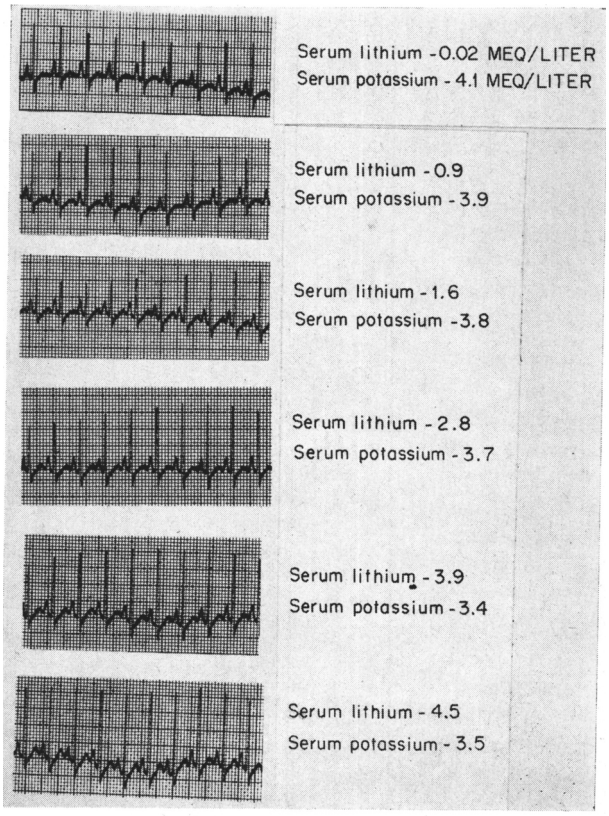

FIG. 2. Serial electrocardiographic rhythm strips from a representative dog obtained during lithium chloride infusion are shown with the values from serum lithium and potassium obtained at the same time. T wave and QRS voltage increases, as does sinus rate (188 to 200), but no conduction delays, QRS or T wave abnormalities are present.

on digitalis glycosides. In this regard, recent electrophysiologic studies of single myocardial cells demonstrate that ouabain toxicity produces progressive reduction in action potential duration, plateau, amplitude, resting membrane potential and conduction velocity (23). Although lithium also decreases resting membrane potential and conduction velocity, it has an opposite effect on action potential duration and also increases the effective refractory period (22). Our experimental model does not add any information to resolve these issues, and studies are currently planned using microelectrode and tissue culture preparations to evaluate these effects further.

We recognize the possibility that barbiturate-induced enzymes, relative to anesthetizing the animals with pentobarbital, may have caused an increase in glycoside metabolism (24) and thereby account for the reduction in arrhythmia duration; however, this seems unlikely, since an increased amount of ouabain was required on the second administration in only three of the nine studies, and in general, sustained arrhythmias were produced by the same dose in the other animals.

These studies suggest that lithium may have important antiarrhythmic properties, especially in the ouabain-induced arrhythmia experimental model which we used, and these may occur through altered catecholamine metabolism or through its direct electrophysiologic effects.

Summary. Epidemiologic studies have shown that residents of hard drinking water areas have a lower mortality due to cardiovascular disease, both in the United States and Britain. It has been postulated that the high lithium content of the hard water may account for this difference by providing a protective effect from lethal arrhythmias. We have studied the effect of iv lithium chloride on ouabain-induced arrhythmias in dogs. The dose required to develop a sustained arrythmia and the total time of the arrhythmia were determined in six dogs. One week later ouabain was given in the same manner to produce a sustained arrhythmia, allowing each dog to serve as its own control. At the onset of the arrhythmia, a continuous infusion of lithium chloride was started (0.5 mEq/min). This resulted in serum levels ranging from 2.6 to 7.8 mEq/liter. The arrhythmia was significantly shortened by administration of the lithium (140 min to 69 min mean; $p < 0.005$), without significant changes in pH, pO_2, serum Na or K. It is concluded that lithium chloride is capable of significantly shortening ouabain-induced arrhythmias.

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