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EFFECT OF THERAPEUTIC DOSAGE OF LITHIUM ON THE HEART

P. DUMOVIC,* G.D. BURROWS & K. CHAMBERLAIN
Department of Psychiatry, University of Melbourne, Parkville, Australia

J. VOHRA, J. FULLER & J.G. SLOMAN
Department of Cardiology, Royal Melbourne Hospital. Australia

1 The cardiac effects of therapeutic levels of lithium were investigated in six healthy male volunteers. Subjects were studied: (1) before lithium ingestion, and (2) when steady-state plasma lithium levels were attained (at least 2 weeks after beginning daily lithium ingestion).

2 A 12-lead electrocardiogram (ECG) and high-speed high-fidelity ECG were used to record electrical activity of the heart. Fractional shortening of the left ventricle using echocardiography, and systolic time intervals (at rest and during exercise), were used as measures of myocardial performance.

3 In this group of healthy volunteers administration of lithium carbonate was associated with a reduction in T wave amplitude in standard electrocardiograms but no statistically significant impairment of myocardial performance.

Introduction

Cardiac side effects of lithium therapy are said to be on the whole infrequent, benign and reversible (Tilkian, Schroeder, Kao & Hultgren, 1976a; Wren & Dana, 1976). Nevertheless, there have been a number of case reports of the effects of lithium on the heart. Five types of effects have been noted. They are (in order of decreasing frequency of occurrence): (1) T wave changes in the electrocardiogram (Andreani, 1957; Schou, 1962; Demers & Heninger, 1970, 1971; Kochar, Wang & D'Cunha, 1971; Hansen & Amdisen, 1978), (2) sinus node abnormalities (Eliasen & Andersen, 1975; Wellens, Cats & Düren, 1975; Wilson, Kraus, Bailas & Rakita, 1976; Roose, Nurnberger, Dunner, Blood & Fieve, 1979), (3) ventricular arrhythmias (Tseng, 1971; Tangedahl & Gau, 1972; Jaffe, 1977), (4) two cases of myocarditis (Tseng, 1971; Swedberg & Winblad, 1974), and (5) one recent case of prolongation of the Q-T interval during lithium toxicity (Jacob & Hope, 1979).

There have been few reported prospective studies of the effects of therapeutic doses of lithium on the electrocardiogram or myocardial function. This paper describes a study of the effects of therapeutic levels of lithium on the electrocardiogram and left ventricular function, in six healthy volunteers, following daily ingestion of lithium carbonate for at least 2 weeks. A high-speed high-fidelity electrocardiogram (Heissenbuttel & Bigger, 1970) and a standard 12-lead ECG have been used to record electrical activity of the heart. Echocardiography of the left ventricle and systolic time intervals at rest and during exercise have been used to record left ventricular performance.

* Present address: Medical Department, Ciba-Geigy Ltd, Basel, Switzerland.

Methods

Subjects and drug administration

Six healthy male volunteers, ages 18 to 23 years were selected. None of the subjects were on any other medication. Each gave his informed consent and the trial was approved by the hospital ethics committee. There was no history of cardiovascular disease and physical examination revealed no abnormalities. Lithium carbonate (Lithicarb, Protea) was taken orally at 09.00 h and 21.00 h at a dosage of between 1,250 mg and 2,000 mg per day for at least 2 weeks. Dosage was controlled by monitoring plasma lithium concentrations in the range of 0.8 to 1.2 mM. A venous blood sample (20 ml) was collected three times a week in the morning 12 h after the previous dose. Both plasma and erythrocyte lithium concentrations were determined by atomic absorption spectrophotometry using a method adapted from that described by Frazer, Secunda & Mendels (1972).

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Electrocardiogram and high-speed electrocardiogram

A standard 12-lead ECG and a high-speed high-fidelity ECG were recorded prior to lithium and after 2 weeks of daily ingestion of lithium carbonate. A venous blood sample (10 ml) was collected at these times and analysed for serum electrolytes. The 12-lead ECG was examined for repolarization changes and rhythm disturbances. T wave heights were measured to the nearest 0.5 mm over several cycles and the mean heights calculated for leads I, V2 and V6 for each subject.

The high-speed ECG was monitored using limb and /or chest leads (usually leads I, II and V_5). The tracings were observed on an oscilloscope screen and recorded on light-sensitive paper at 1000 mm s^{-1} using a Honeywell 858 Visicorder. The high-speed ECG was utilized to accurately measure the QRS duration in the electrocardiogram. Five to ten complexes were measured and the mean was taken.

Echocardiogram of the left ventricle

Subjects were studied before lithium and after two weeks of lithium ingestion. Left ventricular echocardiograms were recorded on a stripchart recorder (SKI-Ekoline 21) using a 2.25 MHz transducer connected to an Ekoline 20A ultrasonoscope. Subjects were examined recumbent and the transducer was placed perpendicular to the surface in the third or fourth left intercostal space, and the ultrasonic beam was directed posteriorly and somewhat laterally and inferiorly.

An index of the extent of myocardial contraction, fractional shortening of the left ventricle, was calculated using the formula:

$$\frac{LVID_d - LVID_s}{LVID_d} \times 100$$

$LVID_d$ is the diastolic left ventricular internal dimension, and was taken at the peak of the R wave in the ECG. $LVID_s$ is the systolic left ventricular internal dimension, and was taken at that point corresponding to the peak downward motion of the interventricular septum (Feigenbaum, 1976).

Systolic time intervals at rest and during continuous dynamic exercise

Subjects were studied at rest and during uninterrupted exercise on a bicycle of constant rate and variable load (Van der Hoeven, Beneken & Clerens, 1973). Measurements were made before lithium and after 2 weeks of lithium ingestion at the same time of the day. Recordings of carotid pulse wave, electrocardiogram and phono-cardiogram were made on a 4-channel (Sanborn) recorder at 100 mm s^{-1}.

The first recording was made with the subject seated at rest, then pedalling continuously at 5, 25, 50, 75 Watt steps; increasing each minute by 25 Watt steps. Recordings were made at the end of each minute when a 'steady-state' was reached. Exercise was continued to maximum performance.

The ECG was taken from two leads—the first a bipolar lead from the manubrium to V_5, and the second from the manubium to V_8 at the inferior angle of the left scapula. The phonocardiogram was recorded by a transducer (Hewlett-Packard) positioned on the second left intercostal space and held there by rubber strapping around the chest and over the left shoulder. The carotid pulse recording was made with a transducer (Hewlett-Packard) positioned over the right carotid artery and held in place by a soft cervical collar.

The systolic time intervals; electromechanical systole (QS_2), left ventricular ejection time (LVET) and pre-ejection period (PEP) were measured in 5–10 cycles at rest and during each work load.

The resting values for the systolic time intervals were transformed into index (I) values (and therefore corrected for heart rate) as described by Lewis, Rittgers, Forester & Boudoulas, 1977).

The QS_2 and LVET values obtained during exercise were plotted as functions of heart rate of each individual and the regression equations thus obtained were used to calculate standard values at a heart rate of 150 beats/min. As Van der Hoeven, Clerens, Donders, Beneken & Vonk (1977) reported, PEP during exercise shows a better linear relationship with the R-R interval than with heart rate. PEP was therefore plotted against the R-R interval and its standard value obtained from the regression lines at R-R equal to 400 ms.

Statistical analysis

The Wilcoxon signed rank test (Siegel, 1956) was used to assess statistical significance, unless otherwise indicated. Comparison of two regression lines was done using the method outlined by Davies & Goldsmith (1972).

Results

Lithium levels

All subjects were on a stable dose after 2 weeks and their plasma levels were within the therapeutic range. Plasma and erythrocyte levels measured on the day of the second set of cardiac tests are listed in Table 1 with the plasma potassium levels for that day.

Table 1 The effect of lithium (Li^+) on T wave amplitude in the electrocardiogram

Subject	*Age (years)*	*Weight (kg)*	*Plasma potassium (mM)*	*Lithium levels (mM)*		*Mean T wave heights (mm)*	
				Plasma	*RBC*	*Pre-Li⁺*	*Li⁺*
1	20	56	3.4	1.13	0.50	4.0	2.3
2	18	67	3.8	1.03	0.41	4.0	2.7
3	22	71	4.1	0.94	0.43	4.0	2.0
4	20	81	3.6	0.97	0.54	4.8	4.5
5	23	61	4.0	0.86	0.47	3.7	3.5
6	18	67	3.4	1.05	0.59	3.0	1.8
mean	20	67	3.7	1.00	0.49	3.9	2.8

Electrocardiogram

Repolarization T wave heights were measured in three representative leads of the standard 12-lead electrocardiogram (I, V2 and V6). There was a statistically significant reduction in T wave height for each of these leads after lithium ($P < 0.05$, paired two-tailed t-test). The means of the three leads for each subject have been listed in Table 1. T-wave reduction occurred in all subjects but was slight for two subjects (4 and 5) and greater than 30% for the rest. No statistically significant correlations were found between the extent of T-wave flattening and either lithium or potassium levels.

QRS interval The effect of lithium on the QRS interval in the electrocardiogram is presented in Table 2. Lithium had no significant effect on QRS duration.

Left ventricular performance

Fractional shortening The effect of lithium on left ventricular performance as assessed by fractional shortening of the left ventricle, is presented in Table 2. Lithium had no significant effect on fractional shortening.

Systolic time intervals The effects of lithium on QS_2I, LVETI, PEPI, and the ratio PEP/LVET recorded at rest are presented in Table 3. Lithium had no statistically significant effect on the systolic time intervals corrected for heart rate or on the ratio PEP/LVET.

The effects of lithium during exercise at a heart rate of 150 b/min on QS_2, LVET, PEP and the ratio PEP/LVET are presented in Table 4. Lithium had no statistically significant effect on any of these parameters.

The LVET before and during lithium ingestion for the six subjects is presented in Figure 1 as a function of heart rate during exercise. No statistically significant differences were found between the means at each exercise load or between the total pooled data sets summarised by the two regression lines.

Similarly the PEP values during exercise have been presented as a function of the R-R interval in Figure 2. Again the two sets of data points were not found to be significantly different.

Maximum exercise performance

After taking lithium for 2 weeks, the subjects were able to attain the same maximum exercise loads and maintain them for the same periods of time.

Discussion

In recent years there has been growing interest in the cardiovascular side effects of drugs used in the treatment of depression. While there have been many publications on the cardiovascular effects of therapeutic and toxic doses of tricyclic antidepressant drugs, there are relatively few reports regarding the effects of lithium on the heart and circulation.

Many of the previous case reports of electrocardiographic abnormalities during lithium carbonate treatment have described effects seen in patients under long-term lithium therapy, often with plasma levels in the toxic range. In addition, many of these patients have been under medication with other drugs. The subjects in the present investigation were

Table 2 The effect of lithium (Li^+) on QRS interval in the electrocardiogram and fractional shortening of the left ventricle.

Subject	*QRS interval (ms)*		*% fractional shortening*	
	Pre-Li⁺	*Li⁺*	*Pre-Li⁺*	*Li⁺*
1	88	80	26	30
2	100	107	29	26
3	86	87	32	33
4	83	84	31	32
5	98	103	30	37
6	76	85	42	40
Mean	88	91	32	33

Table 3 The effect of lithium (Li^+) on QS_2I, LVETI, PEPI and PEP/LVET recorded at rest.

Subject	*QS_2I (ms)*		*LVETI (ms)*		*PEPI (ms)*		*PEP/LVET*	
	Pre-Li^+	*Li^+*	*Pre-Li^+*	*Li^+*	*Pre-Li^+*	*Li^+*	*Pre-Li^+*	*Li^+*
1	506	509	383	363	123	146	0.36	0.51
2	502	508	369	370	133	138	0.42	0.47
3	524	520	396	381	128	138	0.35	0.42
4	508	496	356	352	152	144	0.50	0.48
5	532	501	364	363	170	139	0.63	0.48
6	491	484	363	359	128	125	0.43	0.40
Mean	511	503	372	365	139	138	0.45	0.46

Table 4 The effect of lithium (Li^+) during exercise at a heart rate of 150 beats/min on QS_2, LVET, PEP and PEP/LVET.

Subject	*QS_2 (ms)*		*LVET (ms)*		*PEP (ms)*		*PEP/LVET*	
	Pre-Li^+	*Li^+*	*Pre-Li^+*	*Li^+*	*Pre-Li^+*	*Li^+*	*Pre-Li^+*	*Li^+*
1	245	235	193	175	48	61	0.25	0.35
2	246	247	194	189	52	57	0.27	0.30
3	256	255	208	208	48	48	0.23	0.23
4	260	246	199	191	60	55	0.30	0.29
5	234	236	172	176	62	61	0.36	0.35
6	232	250	185	202	47	48	0.25	0.24
Mean	246	245	192	190	53	55	0.28	0.29

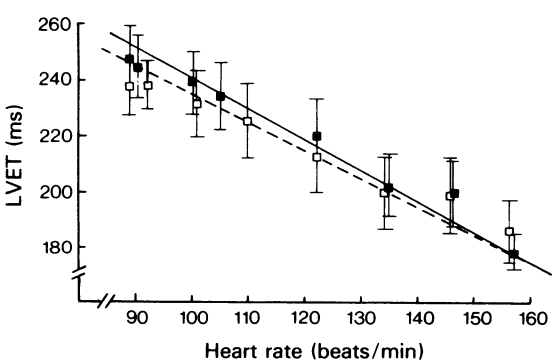

Figure 1 Relationship between LVET and heart rate measured during exercise. The means and the standard errors of the means have been plotted for each exercise load up to 175 Watts ($n=6$ for each point). The regression lines for the pooled data points are also given. The prelithium data is represented by the solid symbols while the open squares and the dotted line represent the data obtained after 2 weeks on lithium.
—$y = 350 - 1.10\ x$, $r = -0.90$, - - - $y = 336 - 1.01\ x$, $r = -0.89$.

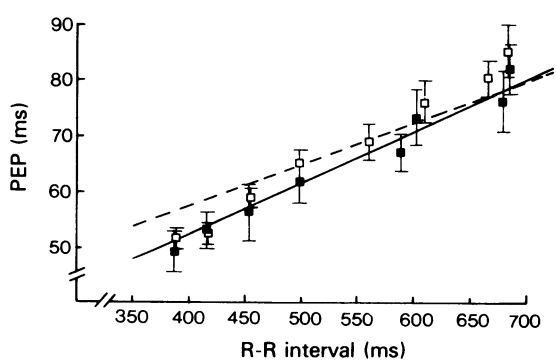

Figure 2 Relationship between PEP and the R-R interval measured during exercise. The means and the standard errors of the means have been plotted for each exercise load up to 175 Watts ($n=6$ for each point). The regression lines for the pooled data points are also given. The prelithium data is represented by the solid symbols while the open squares and the dotted line represent the data obtained after 2 weeks on lithium.

$-y = 0.092\ x + 15.5$, $r = 0.81$, - - - $y = 0.074\ x + 27.7$, $r = 0.72$.

free of other drugs and after daily lithium ingestion for two weeks had plasma lithium levels within the normal therapeutic range (0.8–1.2 mM).

All of the subjects showed some degree of T-wave flattening in the standard electrocardiograms and the effect was clearly noticeable in four of the six subjects. This T-wave flattening is thought to be caused by intracellular hypokalemia that occurs because lithium readily enters cardiac cells but is removed slowly, thus replacing some of the intracellular potassium. This intracellular depletion of potassium may occur even with normal plasma potassium levels (Reisberg & Gershon, 1979). Plasma potassium levels in the six subjects (mean = 3.7 mM) tended to be at the lower end of the normal range (3.5–5.5 mM). However, no significant correlations were found between potassium or lithium levels and the extent of T-wave flattening.

Tilkian, Schroeder, Kao & Hultgren (1976b) found that lithium did not affect maximal exercise performance in a group of psychiatric patients. This observation is supported by the results of the present study. Several subjects showed changes in some of the other cardiac parameters measured. Subject 1, in particular, showed a reduction in myocardial performance after lithium as shown by prolongation of the PEP measured at the heart rate of 150 beats/min. This change, however, did not reflect a systematic trend in the other subjects. Overall, both the systolic time intervals and fractional shortening of the left ventricle, employed as measures of left ventricular performance, revealed no statistically significant effect of lithium on myocardial function.

It needs to be emphasized that this study involved a small number of healthy male subjects and older patients or patients with pre-existing cardiac disease may react differently to lithium. This aspect requires further investigation.

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