Pharmacodynamics and pharmacokinetics of digoxin in the presence of lithium

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- 1 Previous biochemical and clinical data suggest there may be an interaction between digoxin and lithium.
- 2 The pharmacodynamics and pharmacokinetics of an intravenous infusion of digoxin were studied in six male subjects before and after 2 weeks treatment with lithium carbonate.
- 3 The effects of lithium on sodium pump activity, intracellular electrolytes and extracellular electrolytes were studied.
- 4 No significant interaction between digoxin and lithium was found.
- 5 No significant effects of lithium on sodium pump activity or electrolyte concentrations were found.

Keywords digoxin lithium pharmacokinetics pharmacodynamics

Introduction

Lithium carbonate is now extensively used in the treatment of recurrent affective disorders and increasing numbers of patients receiving this now fall into the age group when they may develop cardiovascular disease requiring treatment with digoxin. There is theoretical potential for a drug interaction as these substances have opposite effects on cell membrane $\text{Na}^+ - \text{K}^+$ -adenosine-triphosphatase ($\text{Na}^+ - \text{K}^+$ -ATPase), lithium increasing its activity in manic depressive patients, (Naylor *et al.*, 1977) and digoxin inhibiting it (Schou, 1965). Indeed their effects on $\text{Na}^+ - \text{K}^+$ -ATPase may account for the clinical actions of both drugs (Naylor *et al.*, 1976; Schwartz, 1976). Chambers *et al.* (1982) have suggested a detrimental effect of digoxin on the improvement of manic patients treated with lithium carbonate.

The effect of lithium on the cardiovascular responses to digoxin has not previously been studied. We have examined the effect of digoxin on systolic time intervals of the left ventricle (STIs) and on indices of sodium pump activity in the presence and absence of lithium.

Method

Six healthy male volunteers gave written, informed consent for the study, which was approved by the University Ethical Committee. Mean age of the subjects was 22 years (range 18–34 years), mean height 181 cm, mean weight 74.1 kg. The duration of the study in each subject was 5 weeks.

On the first day of the first week, a 30 ml venous blood sample was drawn at 09.00 h for estimation of serum and intracellular electrolytes and studies of rubidium uptake (methods below). Baseline STIs were recorded at 09.30 h following a 20 min rest. STIs were measured by simultaneous fast speed recordings (100 mm/s) of the ECG, phonocardiograph and carotid artery pulse tracing. Results were based on the mean of 10 consecutive intervals, each corrected for heart rate (Weissler *et al.*, 1972). Following this an intravenous infusion of 750 μg of digoxin was given in 20 ml of normal saline over 20 min using a constant rate infusion pump. Further STIs were recorded at 30 min, 2, 4 and 6 h from the beginning of the infusion. Venous blood samples, for estimation of plasma digoxin con-

centrations, were withdrawn from an indwelling cannula before, halfway through and at the end of the infusion and thereafter at 10, 20, 30, 45 and 60 min, and at 2, 3, 4, 5, 6 and 12 h from the end of the infusion.

On the following 4 days the subjects returned each morning and at 09.00 h, again following a 20 min rest, STIs were recorded and a further blood sample drawn for plasma digoxin estimation. A collection was made of all urine passed during each of the first 5 days of the study. For Day 1 this was obtained as two 12 h samples and for Days 2–5 as one 24 h sample each. Urine volumes and digoxin concentrations were measured.

The last 2 days of the first week and the whole of the second week formed a 'digoxin-washout' period. On the first day of the third week subjects all took 600 mg of lithium carbonate (Priadel, Delandale) and, following a serum lithium estimation 24 h later, were assigned a daily dose of lithium carbonate expected to give a steady-state serum level in the region of 0.6–1.2 mmol/l (Cooper & Simpson, 1976). The daily dose was in fact 800 mg twice daily, taken at 09.00 h and 21.00 h, for all subjects. Serum lithium concentrations were estimated every 3 days following this, until the end of the fourth week, to ensure that the desired serum level was reached and that toxic levels did not occur.

On the first day of the fifth week (after 2 weeks of lithium treatment) venous blood was drawn at 09.00 h for estimation of serum and intracellular electrolytes and studies of rubidium uptake. At the same time a sample was taken for serum lithium estimation, omitting that morning's dose. Baseline STIs were measured and an intravenous infusion of digoxin given, followed by repeated measurement of STIs and withdrawal of venous samples for plasma digoxin estimation, as on the first day of the study. The other procedures of the first week were repeated with the addition of a venous blood sample for serum lithium each morning. Subjects continued to take their lithium carbonate throughout this final week, taking the morning dose after attendance at the investigation unit.

Serum electrolytes and serum lithium were estimated by standard flame photometric methods after appropriate dilutions. Intracellular electrolytes were similarly estimated after the red blood cells were washed three times in isotonic magnesium chloride and then lysed in hypotonic buffer. Plasma digoxin and urinary digoxin concentrations were estimated by radioimmunoassay (Gammadisk, Wellcome Reagents). Rubidium studies were performed on erythrocytes separated by centrifugation and washed in potassium-free Ringer solution. Two

sets of Erlenmeyer flasks were prepared with potassium-free Ringer solution and 0.5 ml washed erythrocytes. To one set a series of concentrations of digoxin was added and to the other set a fixed concentration of digoxin and a series of concentrations of frusemide. These were incubated by shaking for 2 h at 37° C and then rubidium 86 (⁸⁶Rb; Amersham) was added to produce a final concentration in each flask of 5 μ M. The incubation was continued for a further hour. Portions of the cell suspensions were then removed and, after addition of solubiliser and a scintillation cocktail, radioactivity was counted in a liquid scintillation counter. Absolute and digoxin sensitive ⁸⁶Rb uptake were calculated as well as the ability of digoxin and frusemide to inhibit the respective digoxin sensitive and insensitive portions of rubidium uptake (Kelly *et al.*, 1983).

The means and s.e. means are reported for pre- and post-lithium administration measurements and the significance of differences between the means was tested using paired *t*-tests.

Results

All subjects had reached steady state serum lithium levels on the seventh day after commencing lithium carbonate. Mean steady state level was 0.76 mmol/l (range 0.40–1.00 mmol/l). Mean half-life, clearance and volume of distribution of digoxin were not significantly altered by lithium (Table 1).

Lithium treatment for 2 weeks did not produce any significant change in mean erythrocyte ⁸⁶Rb uptake, the percentage of this sensitive to digoxin, the percentage uptake or the 50% inhibiting concentrations of digoxin and frusemide (Table 2). Serum and intracellular electrolytes were unaffected by chronic lithium treatment (Table 3). Chronic lithium treatment did not significantly affect baseline P-R, QRS and QTc intervals measured before digoxin infusion (Table 4). None of the baseline STI estimates showed significant change (Table 4). Table 5 describes the pharmacodynamic effect of digoxin, giving the mean maximum changes induced in the cardiac parameters by the infusion. None of these mean maximum changes were influenced by chronic lithium treatment.

Results were examined for possible correlations between biochemical parameters and the cardiac pharmacodynamic parameters. A significant correlation between change in the percentage of ⁸⁶Rb uptake sensitive to digoxin and the change in QTc, following lithium emerged $r = -0.892$, $P < 0.05$; Figure 1).

Table 1 Effect of lithium on digoxin pharmacokinetics.

	<i>Pre-lithium</i>	<i>Post-lithium</i>
Mean half-life (h)	45.8 ± 2.8	41.7 ± 4.4
Clearance (ml/min)	109.5 ± 6.3	122.3 ± 14.9
Volume of distribution (l)	438 ± 26	423 ± 39

Table 2 Effect of lithium on ^{86}Rb uptake.

	<i>Pre-lithium</i>	<i>Post-lithium</i>
^{86}Rb Uptake (mmol ml ⁻¹ cells h ⁻¹)	3.6 ± 0.5	3.1 ± 0.6
% ^{86}Rb uptake digoxin sensitive	59.7 ± 4.1	56.4 ± 5.0
50% inhibitory digoxin concentration (nM)	6.1 ± 0.5	5.7 ± 0.5
50% inhibitory frusemide concentrations (mM)	0.044 ± 0.002	0.044 ± 0.003

Table 3 Effect of lithium on electrolytes (mmol/l, mean ± s.e.mean).

	<i>Pre-lithium</i>	<i>Post-lithium</i>
Serum Na ⁺	143.0 ± 3.3	140.0 ± 2.7
Serum K ⁺	4.8 ± 0.2	4.4 ± 0.1
Erythrocyte Na ⁺	7.8 ± 0.9	8.3 ± 1.2
Erythrocyte K ⁺	71.0 ± 3.7	76.0 ± 3.9

Table 4 Cardiac effects of lithium (mean ± s.e. mean).

	<i>Pre-lithium</i>	<i>Post-lithium</i>
P-R (s)	0.16 ± 0.01	0.16 ± 0.01
QRS (s)	0.09 ± 0.00	0.10 ± 0.00
QTc (s)	0.40 ± 0.01	0.43 ± 0.01
PEP (ms)	109 ± 5	109 ± 5
LVET (ms)	314 ± 11	292 ± 12
PEP/LVET	0.35 ± 0.02	0.37 ± 0.02
QA ₂ (ms)	424 ± 12	413 ± 14

Table 5 Effect of lithium on the pharmacodynamics of digoxin (means ± s.e. mean of maximum changes, (ms), following digoxin infusion).

	<i>Pre-lithium</i>	<i>Post-lithium</i>
Δ QTc	0.06 ± 0.01	0.02 ± 0.02
Δ PEP	8.7 ± 5.5	6.7 ± 5.5
Δ LVET	17.2 ± 3.9	10.7 ± 5.7
Δ PEP/LVET	0.03 ± 0.03	0.04 ± 0.04
Δ QAc	34 ± 5	33 ± 4

Figure 1 Correlation between change in the percentage of erythrocyte ⁸⁶Rb uptake sensitive to digoxin and the change in QT_c interval following lithium carbonate treatment.

Discussion

These results do not suggest any significant pharmacokinetic or pharmacodynamic interaction between lithium, at commonly used 'therapeutic' plasma levels, and digoxin in healthy young male subjects and would suggest that this drug combination may be without serious risk. Our result disagrees with that of Chambers *et al.* (1982) who found during a 1 week, double-blind trial of digoxin or placebo, in addition to lithium, for mania that digoxin impaired the response to lithium. It may be, as the above authors concede in their paper, that the chlorpromazine allowed to the patients, though not differing in amount between the two groups, might have affected the result. However, Naylor *et al.* (1977) failed to find any effect of lithium on Na⁺-K⁺ ATPase activity in healthy subjects, which could explain our inability to find any interaction. Though a decrease in Na⁺-K⁺ ATPase activity has been found in patients suffering from affective disorders (Naylor *et al.*, 1980; Whalley *et al.*, 1980) this is not a universal finding (Akagawa *et al.*, 1980; Sengupta *et al.*, 1980) and may be related to changes in plasma cortisol concentration (Nurnberger *et al.*, 1982). Furthermore, while Naylor *et al.* (1977) have demonstrated an increase in Na⁺-K⁺ ATPase activity in manic-depressive patients following lithium treatment this was not found by Nurnberger *et al.* (1982).

No physiologically important derangement of electrolytes has been noted in patients with affective psychosis, any statistically significant alterations found being small (Coppen, 1965; Frazer *et al.*, 1983). Thus, while it might be suggested that the effects of lithium in patients suffering from affective disorders could be different from those in healthy subjects, evidence in favour of this is not consistent.

The trend in our study was for a decrease in Na⁺-K⁺ ATPase activity in healthy subjects, following lithium, rather than the trend towards an increase as Naylor *et al.* (1977) found. A decrease could account for the synergistic effect between lithium and digoxin in a single patient case report (Winters & Ralph, 1977). This patient was found to have a serum lithium level of 2.0 mmol/l and plasma digoxin level of 0.7 ng/ml and developed a junctional bradycardia of 30 beats/min. Ku *et al.* (1977) found that though lithium stimulated cardiac Na⁺-K⁺ ATPase *in vitro* its action on sodium pump activity in guinea-pig ventricular slices was inhibitory.

Age does not appear to affect the digoxin-sensitive component of ⁸⁶Rb uptake (Kelly *et al.*, 1983), which is the part believed to reflect activity of Na⁺-K⁺ ATPase. It would therefore appear reasonable to extrapolate the results from these young volunteers to patients taking lithium carbonate who would generally be older. The ability of digoxin to inhibit digoxin-sensitive ⁸⁶Rb uptake does increase with age (Kelly *et al.*, 1983) but lithium had no significant effect on this (Table 2). No trends were discernible within the results, some subjects showing no changes in the parameters studied while others showed either increases or decreases, suggesting that study of a larger number of subjects would not have materially changed our conclusions.

The cardiovascular effects of lithium alone have previously been investigated. At 'therapeutic' serum lithium levels the only consistent effect reported is 'T' wave depression. Some authors have suggested this might relate to changes in K⁺ with lithium treatment. The correlation between change in the proportion of the sodium pump activity sensitive to digoxin and the change in QT_c was unexpected but of interest and may suggest that the digoxin-sensitive component of sodium pump activity has a direct relationship to the width of the cardiac action potential.

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