Effect of oral lithium on bronchial reactivity in asthma

A. J. KNOX, B. G. HIGGINS, I. P. HALL and A. E. TATTERSFIELD
Respiratory Medicine Unit, City Hospital, Nottingham, U.K.

(Received 20 June/13 November 1991; accepted 19 November 1991)

1. Recognition that inositol phospholipid-derived second messengers are involved in the initiation and maintenance of airway smooth muscle contraction raises the possibility of new therapeutic approaches to the treatment of asthma. We anticipated that lithium, through its effects on cell signal transduction and ion-transport pathways, would be likely to protect the airways against constrictor stimuli.

2. We carried out a randomized, double-blind study of lithium carbonate in asthmatic patients.

3. After a 1 week run-in period, 27 patients were allocated lithium carbonate (800 mg) or placebo for 21 days with measurement of forced expiratory volume in 1 s, the dose of histamine causing a 20% fall in the forced expiratory volume in 1 s and serum lithium concentration on days 3, 7, 14 and 21.

4. Twenty-one patients completed the study (10 on lithium, 11 on placebo). Mean serum lithium levels for patients on active treatment were in the therapeutic range on all four occasions.

5. Lithium did not alter the forced expiratory volume in 1 s (P=0.8) or the twice-daily peak expiratory flow (P=0.15). It did, however, reduce histamine reactivity (the maximum difference between lithium and placebo was 1.2 doubling doses of histamine on day 21; 95% confidence interval 0.2–2.2 doubling doses), improve symptom scores (P<0.05) and reduce usage of \( \beta \)-adrenoceptor agonist inhalers (P<0.05).

6. We conclude that lithium reduces bronchial reactivity in airway smooth muscle; this finding raises new therapeutic possibilities for the treatment of asthma.

EXPERIMENTAL

Patients

We recruited 27 non-smoking asthmatic men aged 18–45 years, whose asthma was controlled on inhaled therapy alone. All patients were taking \( \beta \)-adrenoceptor agonists and 12 were taking an inhaled corticosteroid. No patient was taking any other asthma medication. All were clinically stable with no history of upper respiratory tract infection within the preceding 6 weeks; all had previously demonstrated an improvement in forced expiratory volume in 1 s (FEV\(_1\)) of >15% after 200 \( \mu \)g of inhaled salbutamol. Patients had to have a provocative dose of histamine that caused a 20% fall in FEV\(_1\) (PD\(_{20}\)) of less than 4 \( \mu \)mol. Written consent was obtained from all patients. The study design was approved by the Nottingham City Hospital Ethics Committee.

Methods

FEV\(_1\) was measured on a dry bellows spirometer (Vitalograph, Buckingham, Bucks, U.K.) taking the higher of two measurements within 100 ml. Histamine challenge was performed by using a modification of the method of Yan et al. [10] using De Vilbiss hand-held nebulizers with an output in the range 0.0025–0.0035 ml/activation. After baseline measurement of FEV\(_1\), subjects inhaled three puffs of 0.9% (w/v) NaCl (saline), with a repeat measurement of FEV\(_1\) 1 min later. Subjects then inhaled increasing doses of histamine in doubling increments over the cumulative dose range 0.03–16 \( \mu \)mol, with a repeat measurement of FEV\(_1\) 1 min after each dose. The test was discontinued when FEV\(_1\) had fallen by 20% from the post-saline value. PD\(_{20}\) was estimated by interpolation on a log dose–response plot.

Subjects were asked to grade their asthma symptoms from 0 to 3 each day: 0, no symptoms; 1, mild symptoms (easily tolerated); 2, moderate symptoms (some interference with daily activities); 3, severe symptoms (unable to carry out usual activities).

Key words: asthma, bronchial reactivity, lithium.

Abbreviations: DD, doubling dose; FEV\(_1\), forced expiratory volume in 1 s; Ins(1,3,4,5)\( P \), inositol 1,3,4,5-tetrakisphosphate; Ins(1,4,5)\( P \), inositol 1,4,5-trisphosphate; PD\(_{25}\), dose of histamine causing a 20% fall in forced expiratory volume in 1 s; PEF, peak expiratory flow.

Correspondence: Dr Alan J. Knox, Respiratory Medicine Unit, City Hospital, Hucknall Road, Nottingham NG5 1PB, U.K.
Serum lithium levels

Venous blood (10 ml) was collected for measurement of the serum lithium concentration by flame emission photometry (IL 745; Instrumentation Laboratory, Warrington, Cheshire, U.K.). An independent investigator monitored serum lithium levels in order to try to maintain levels between 0.5 and 1 mmol [11]. If levels were outside the therapeutic range, the patient was telephoned and asked to alter the tablet dose. In order to keep the study double blind, an equal number of patients on placebo had their medication altered in a similar manner; the principal investigator was unaware of the drug levels or treatment that each patient was taking.

Study design

Patients attended the laboratory on day 1 for initial assessment and measurement of FEV₁ and histamine reactivity. They were given a mini-Wright peak flow meter and asked to record twice-daily peak expiratory flow (PEF; best of three), daily usage of β-adrenoceptor agonist inhalers and daily symptom scores for a week before attending for a second visit for a repeat measurement of FEV₁ and histamine reactivity. They were then randomized to receive either oral lithium carbonate (Delandale, Canterbury, Kent, U.K.) 800 mg at night or matched placebo for 21 days. Measurement of FEV₁, histamine reactivity and serum lithium concentrations were performed on days 3, 7, 14 and 21 of treatment. All visits were made at the same time of day. Twice-daily PEF, daily symptom score and daily usage of β-adrenoceptor agonist inhalers were recorded throughout the study. Patients were instructed to maintain their dose of inhaled corticosteroid at the same level throughout the study. The study was designed so that it had 95% power to detect a difference in bronchial reactivity between active treatment and placebo of 1 doubling dose (DD) of histamine at the 5% level. A parallel groups design was used as it would be difficult to choose a suitable washout period in a crossover study to ensure that any effect of lithium would not be carried over to the placebo period.

Statistical evaluation

Patients available for analysis. Four patients withdrew: one on placebo (chest infection on day 8 that required treatment with prednisolone) and three on lithium (one owing to pressure of work and difficulty in concentrating and two owing to a change in their job). Two further patients were excluded (one from each group) because they had taken inhaled salbutamol within 6 h of their visits to the department. Data analysis was thus confined to the 21 patients who completed the study (10 on lithium, 11 on placebo).

Analyses. PD₂₀ values were log transformed for all analyses. Mean values of FEV₁ and PD₂₀ for each patient on the two visits before randomization were used as baseline. Mean PEF for weeks 1 (before treatment), 2, 3 and 4 were calculated for each subject. The change in PD₂₀ is expressed as DD of histamine [12]. Changes in FEV₁, PD₂₀ and mean PEF after lithium and placebo were compared by analysis of variance by drug by time. Weekly inhaler usage and symptom score (week 1 versus weeks 2–4) were analysed non-parametrically by assigning Fisher–Yates normal scores to the data [13]; changes in these measures were then analysed by analysis of variance by drug by time.

RESULTS

Serum lithium levels

The mean (range) serum lithium levels in patients on active treatment were 0.59 (0.4–0.76), 0.61 (0.4–0.8), 0.62 (0.4–0.8) and 0.55 (0.2–0.8) mmol/l after 3, 7, 14 and 21 days of treatment, respectively. Three patients had their therapy increased to 1200 mg of lithium/day because their serum lithium levels were below 0.5 mmol/l.

Baseline characteristics

The mean (SEM) FEV₁ was 85(3)% of predicted for patients completing the study. Six out of 11 patients in the placebo group and five out of 10 patients in the lithium group were using inhaled steroids. None of the baseline values differed significantly between the two groups (Table 1).

FEV₁, home PEF and histamine reactivity

There was no significant difference in the change in FEV₁ between the lithium and placebo groups (P = 0.8, 95% confidence interval on day 21 −0.49 to +0.42 litres). There was no significant difference in the change in PEF (week 1 versus weeks 2, 3 and 4) between the lithium and placebo groups (P = 0.15, 95% confidence interval for week 3, +57 to −26 litres/s).

Lithium caused a reduction in histamine reactivity when compared with placebo (P < 0.02). The difference between lithium and placebo was maximal at 3 weeks when PD₂₀ was increased on lithium by 1.2 DD of histamine (95% confidence interval 0.2–2.2 DD) compared with placebo. These results are shown in Table 2, Fig. 1 and Fig. 2(a). There was no relationship between peak flow variability (expressed as amplitude % mean) and changes in PD₂₀ in the patients treated with lithium.

Table 1. Baseline values. FEV₁ and PEF are given as means (SEM), PD₂₀ is shown as geometric means (SEM in log units) and weekly symptom score and weekly inhaler usage are presented as means (range).

<table>
<thead>
<tr>
<th></th>
<th>Lithium</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁ (litres)</td>
<td>3.34 (0.3)</td>
<td>3.50 (0.3)</td>
</tr>
<tr>
<td>PEF (litres/s)</td>
<td>503 (25)</td>
<td>531 (24)</td>
</tr>
<tr>
<td>PD₂₀ (µmol)</td>
<td>0.36 (0.24)</td>
<td>0.65 (0.19)</td>
</tr>
<tr>
<td>Weekly symptom score</td>
<td>6.5 (1–14)</td>
<td>5 (0–13)</td>
</tr>
<tr>
<td>Weekly inhaler usage (puffs/week)</td>
<td>12.5 (1–75)</td>
<td>13.5 (0–58)</td>
</tr>
</tbody>
</table>
Effect of lithium on bronchial reactivity

Table 2. Values of different variables during the study. FEV₁ and home PEF are shown as means (SEM). PD₂₀ is given as geometric means (SEM in log units) and weekly symptom score and weekly inhaler usage are presented as medians (range).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Day 3</th>
<th>Day 7</th>
<th>Day 14</th>
<th>Day 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁ (litres)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lithium</td>
<td>3.34 (0.3)</td>
<td>3.36 (0.3)</td>
<td>3.34 (0.3)</td>
<td>3.35 (0.3)</td>
<td>3.42 (0.2)</td>
</tr>
<tr>
<td>Placebo</td>
<td>3.50 (0.3)</td>
<td>3.53 (0.2)</td>
<td>3.55 (0.2)</td>
<td>3.54 (0.3)</td>
<td>3.62 (0.3)</td>
</tr>
<tr>
<td>PD₂₀ (µmol)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lithium</td>
<td>0.36 (0.24)</td>
<td>0.57 (0.19)</td>
<td>0.63 (0.17)</td>
<td>0.55 (0.21)</td>
<td>0.81 (0.21)</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.65 (0.19)</td>
<td>0.66 (0.23)</td>
<td>0.70 (0.24)</td>
<td>0.66 (0.24)</td>
<td>0.63 (0.21)</td>
</tr>
<tr>
<td>Home PEF (litres/s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lithium</td>
<td>503 (25)</td>
<td>514 (24)</td>
<td>523 (21)</td>
<td>521 (20)</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>531 (24)</td>
<td>532 (25)</td>
<td>536 (23)</td>
<td>539 (22)</td>
<td></td>
</tr>
<tr>
<td>Weekly symptom score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lithium</td>
<td>6.5 (1-14)</td>
<td>4 (0-13)</td>
<td>2.5 (0-11)</td>
<td>0.5 (0-11)</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>5 (0-13)</td>
<td>6.5 (2-10)</td>
<td>7 (0-11)</td>
<td>1.5 (0-11)</td>
<td></td>
</tr>
<tr>
<td>Weekly inhaler usage (puffs/week)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lithium</td>
<td>12.5 (1-75)</td>
<td>11.5 (0-68)</td>
<td>2 (0-75)</td>
<td>2 (0-76)</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>13.5 (0-58)</td>
<td>15.5 (0-70)</td>
<td>15.5 (0-76)</td>
<td>12 (0-74)</td>
<td></td>
</tr>
</tbody>
</table>

Symptom score, inhaler usage and side effects

One patient in the placebo group did not complete his diary card properly. Changes in symptom score and inhaler usage were compared in the remaining 20 patients (10 on lithium, 10 on placebo). Symptom score and inhaler usage were significantly reduced (both P< 0.05) from baseline in the lithium group when compared with the placebo group (Table 2, Figs. 2b and 2c). Few adverse effects were recorded. One patient on lithium complained of difficulty in concentration and withdrew through pressure of work. As he was under more stress than usual at work it is not clear whether lithium affected his symptoms or not. One patient on lithium complained of mild diarrhoea, which resolved spontaneously in less than 24 h without a change in therapy.

DISCUSSION

The aim of our study was to determine whether 3 weeks of treatment with lithium would reduce bronchial responsiveness in patients with relatively mild asthma. The serum lithium concentrations we obtained were similar to those used in the prophylactic treatment of manic depressive illness [11]. Lithium caused a significant reduction in bronchial reactivity to histamine with a maximum reduction of 1.2 DD of histamine after 3 weeks of therapy. In addition, lithium improved asthma symptoms and reduced requirements for inhaled β-adrenoceptor therapy. These changes were accompanied by a small but non-significant improvement in home PEF measurements but no improvement in FEV₁. This may be because the patients had relatively mild asthma and there-
Before were less able to demonstrate bronchodilatation than a change in bronchoconstrictor responsiveness.

Four patients were unable to complete the study (three in the lithium group). None of the patients receiving lithium had any deterioration in their asthma symptoms or FEV₁ before withdrawal and it is unlikely therefore that omission of these patients materially affected the results. Baseline characteristics of the patients in the two groups were well matched with respect to FEV₁, PEF, symptom score and inhaler usage; geometric mean PD₂₀ values were lower in the lithium-treated group than in the control group, although this difference was not significant. It seems unlikely that a slightly lower PD₂₀ value would alter the response, since PD₂₀ values in both groups were well below the range seen in normal subjects and the values seen in patients treated with corticosteroids [14].

Several mechanisms need to be considered in order to explain the effects of lithium in our study. The first is that lithium is modulating the inositol phospholipid second messenger system in airway smooth muscle. Muscarinic and histamine H₁-receptor occupation in airway smooth muscle results, via a specific G protein, in the activation of phosphoinositidase C, which hydrolyses phosphatidylinositol 4,5-bisphosphate to produce the two intracellular second messengers, inositol 1,4,5-trisphosphate [Ins(1,4,5)P₃] and diacylglycerol. Ins(1,4,5)P₃ initiates contraction by mobilizing calcium from internal stores [4–6, 15, 16], whereas diacylglycerol is able to activate protein kinase C, which is responsible for maintaining contraction [6, 17, 18]. Ins(1,4,5)P₃ is metabolized to inositol 1-phosphate, which is dephosphorylated by inositol monophosphatase to release free inositol, which is reincorporated into the membrane phospholipid pool. By inhibiting inositol monophosphatase (see Fig. 3), lithium interrupts inositol phosphate recycling and depletes the membrane phospholipid pool, thus impairing the ability of airway smooth muscle cells to initiate and maintain a contractile response [2, 6, 14]. Other possible mechanisms of action of lithium include inhibition of the 3'-kinase responsible for converting Ins(1,4,5)P₃ to inositol 1,3,4,5-tetrakisphosphate [Ins(1,3,4,5)P₄], thus reducing agonist-induced Ins(1,4,5)P₃ and Ins(1,3,4,5)P₄ production [19, 20], and uncoupling of receptors (muscarinic and adrenergic) from their respective G proteins [3], as has been demonstrated with lithium in neuronal tissue. Similar effects on airway smooth muscle would reduce the contractile response to spasmogens such as histamine.

Alternatively, lithium may be altering sodium transport in airway smooth muscle. Treatment of human subjects with lithium for several weeks caused an increase in tissue Na⁺/K⁺-ATPase activity [21]. Activation of Na⁺/K⁺-ATPase in airway smooth muscle would reduce the intracellular sodium concentration, increase calcium extrusion via sodium/calcium exchange and hence reduce contractility [22, 23].

The observation that lithium reduces airway smooth muscle contractility in the guinea-pig at concentrations as low as 0.1 mmol/l suggests that lithium could be acting on airway smooth muscle in our study. The fact that the effects were confined to the airway could be due to inositol phospholipid turnover in airway smooth muscle being increased in asthma owing to excessive stimulation by inflammatory mediators. However, similar cellular signal transduction systems and sodium transporters are found in inflammatory cells and airway epithelium [24–26], so lithium could potentially be reducing bronchial reactivity by reducing mediator release or by modulating epithelial cell function.

Fig. 2. Mean (±SEM) change in PEF (a), median change in weekly symptom scores (b) and median change in inhaler usage (c) in patients on lithium (*) and placebo (○) in weeks 1, 2, 3 and 4.
The effect of lithium on bronchial reactivity

For chronic therapy, lithium may have a place in the treatment of patients with severe asthma that is resistant to other drugs, but this requires further investigation in carefully monitored studies. Further research is needed to determine the precise site of action of lithium on the airway and the role of G proteins, inositol phospholipid metabolism and sodium-transport processes in airway cells.

ACKNOWLEDGMENTS

We thank Mr A. Wisniewski and Mrs S. Cooper for technical help, Dr C. Marenah for determining serum lithium levels, and the Asthma Research Council for providing financial support.

REFERENCES