Granulocyte Function During Lithium Therapy

By Myron S. Cohen, Behnam Zakhireh, Julia A. Metcalf, and Richard K. Root

Random migration, chemotaxis, phagocytosis, and bactericidal ability of neutrophils from 5 patients receiving lithium carbonate were compared with those of neutrophils from healthy donors. These cells functioned normally in all respects. Neither sera from patients receiving lithium carbonate nor the addition of lithium chloride to control cells in vitro significantly altered their functional capacity. These findings suggest that neutrophil function in patients receiving lithium therapy is preserved, and they support the potential utility of this drug as a leukopoietic agent in neutropenic states.

Therapy with lithium carbonate often produces granulocytosis in psychiatric patients, and it has recently been used to offset the neutropenia associated with cancer therapy. If lithium carbonate is to prove useful in the treatment of neutropenic states, it is important to examine the functional capacities of cells from patients receiving the drug. Accordingly, we studied several in vitro functions of neutrophils from patients receiving lithium carbonate, as well as cells exposed to lithium chloride in vitro.

MATERIALS AND METHODS

Lithium carbonate (Lithane) obtained from Roerig (New York, N.Y.) was administered therapeutically to 5 patients with depressive disorders. There were 4 women and 1 man whose ages ranged from 20 to 51 yr. All patients had received lithium for at least 8 wk before the study. Their dosages ranged from 0.68 to 1.7 g/day, with a mean of 1.2 ± 0.21 g/day. This resulted in serum lithium concentrations ranging from 0.68 to 1.7 mEq/liter, with a mean of 1.2 ± 0.21 mEq/liter.

Leukocytes

Subsequent to serum lithium determination, neutrophils from both patients and normal volunteers were obtained by dextran sedimentation and hypotonic lysis of contaminating erythrocytes. Leukocyte counts from whole blood of patients receiving lithium carbonate were performed with a Coulter counter (Coulter Electronics, Hialeah, Fla.). Differential counts were performed by examination with Wright stain.

Phagocytosis and Bactericidal Activity

The phagocytic activities of PMNs at 10 and 20 min were assessed as previously described by determining the uptake of Staphylococcus aureus 502A radiolabeled with a mixture of 14C-labeled amino acids. Bacterial counts were adjusted to allow a 500:1 particle:cell ratio and hence maximally stress the phagocytic capacity of the neutrophils. The abilities of PMNs to kill S. aureus 502A at 20, 30, and 60 min were determined by a method previously described. Bacterial counts were adjusted to allow a 10:1 particle:cell ratio.
Locomotion

Random migration and chemotaxis were evaluated by the modified Millipore-Boyden chamber technique using Gey’s buffer in random migration and 5% endotoxin (Escherichia coli 0127:B8, lipopolysaccharide B, Difco Laboratories, Detroit, Mich.) activated serum in chemotaxis assays.

Experimental Design

In all assays, patient cells were compared with simultaneously run control normal cells in preparations containing either patient or control normal serum. The in vitro effects of lithium were determined by incubating control cells in 10% normal serum-HBSS with lithium chloride (Fisher Scientific, Fair Lawn, N.J.) for 30 min at final concentrations of 0.5 mM and 2.0 mM. All assays were performed in duplicate.

RESULTS

Leukocyte counts among the 5 psychiatric patients ranged from 8,300 to 14,500/cu mm, with absolute granulocyte counts (segmented forms and band forms) of 6,300–11,400/cu mm. Three of the 5 patients had leukocyte counts greater than 10,000/cu mm. The functional capacities of patient cells are shown in Tables 1 and 2. Phagocytosis and killing by cells from patients receiving lithium were equivalent to those of control cells in either control or patient serum, as were random migration and chemotaxis. Phagocytic rates of both patient and control cells were slightly increased in the sera of patients taking lithium (132.4 ± 17.8% and 111.6 ± 5.8% mean ± SEM compared with patient and control cells, respectively in control sera); however, the increases were not statistically significant. Cells from the 3 patients with leukocyte counts greater than 10,000/cu mm were identical in function to those of the 2 patients without leukocytosis. Exposure of cells from healthy volunteers to lithium chloride in vitro did not alter chemotaxis, bactericidal capacity, or phagocytosis (total of three experiments).

DISCUSSION

Neutropenia is associated with infection, and any agent that reverses this condition is potentially therapeutically important. Lithium carbonate appears to increase not only the blood neutrophil concentration but also the marrow reserve and total neutrophil pool. MacGregor and Dyson recently reported that granulocytes obtained from patients receiving lithium exhibited decreased adherence to nylon-wool fibers. This effect was not mediated directly by lithium, and adherence improved significantly with dialysis of plasma. Since adherence to venule walls appears to be an important step in the ability of neutrophils to leave the circulation.

| Table 1. Effects of Li$_2$CO$_3$ Therapy on the Function of Patient Neutrophils* |
|----------------|----------------|----------------|----------------|----------------|----------------|
| Serum Source   | Phagocytic Activity of Patient Cells† | Bactericidal Ability of Patient Cells† | Chemotaxis of Patient Cells† |
|                | 10 min           | 20 min           | 20 min           | 30 min           | 60 min           |
| Normal sera    | 102.6 ± 0.4      | 101 ± 8.5        | 116.2 ± 23.6     | 98.8 ± 15        | 100 ± 0.44       | 111.0 ± 8.5      |
| (100% = normal cells and normal sera) |                  |                  |                  |                  |                  |                  |
| Patient sera   | 119.4 ± 0.99     | 109.6 ± 12.3     | 119.4 ± 21.9     | 87.8 ± 1.24      | 99.6 ± 0.4       | 113.0 ± 5.9      |
| (100% = normal cells and patient sera) |                  |                  |                  |                  |                  |                  |

*Values given are means ± SEM of percentage of control. The control for patient cells in normal serum was normal cells in normal serum. The control for patient cells in patient serum was normal cells in patient serum. Neutrophils from 5 patients and 5 normal volunteers were compared.
†No parameters compared were statistically significantly different using the paired t test.
Table 2. Effects of Serum From Lithium-Treated Patients on the Function of Normal and Patient Neutrophils

<table>
<thead>
<tr>
<th>Cell Source</th>
<th>Phagocytosis in Patient Serum</th>
<th>Bactericidal Ability in Patient Serum</th>
<th>Chemotaxis in Patient Serum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal cells</td>
<td>111.6 ± 5.8, 96 ± 5.8</td>
<td>97 ± 3.0, 99.4 ± 6.8</td>
<td>100.2 ± 0.37, 98.6 ± 2.1</td>
</tr>
<tr>
<td>Patient cells</td>
<td>132.4 ± 17.8, 104 ± 9.3</td>
<td>102.4 ± 4.7, 101.1 ± 3.1</td>
<td>101 ± 2.37, 101.2 ± 4.6</td>
</tr>
</tbody>
</table>

*Values given are means ± SEM of percentage of control. The control for normal cells in normal serum was normal cells in normal serum. The control for patient cells in patient serum was patient cells in normal serum. Neutrophils from 5 patients and 5 normal volunteers were compared. No parameters compared were statistically significantly different using the paired t test.

and enter inflammatory sites, depression of adherence in vivo by lithium may adversely affect the inflammatory response. In contrast to these findings, Rothstein and his colleagues reported increased migration into inflammatory sites in patients receiving lithium. A normal ability of cells from lithium-treated patients to ingest yeast has also been described. Our studies have substantially extended these in vivo observations on neutrophil function.

We found normal neutrophil random migration, chemotaxis, phagocytosis, and bactericidal ability regardless of leukocyte count in 5 patients receiving lithium carbonate. Sera from patients receiving lithium did not significantly alter cell function in control cells. Addition of lithium chloride to normal neutrophils had no adverse effects on cell functions. These findings suggest that during lithium carbonate therapy neutrophils may be expected to contribute normally to the host defense system. The overall utility of lithium carbonate as a neutropoietic agent remains to be determined.

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REFERENCES

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