CONCISE REPORT

Lithium Is an Ineffective Therapy for Human Cyclic Hematopoiesis

By W. P. Hammond, B. Berman, D. G. Wright, and D. C. Dale

Cyclic hematopoiesis is a rare disease in man in which severe neutropenia recurs at 21-day intervals with associated illness. Because lithium carbonate therapy has been shown to eliminate cyclic hematopoiesis in grey collie dogs, we examined the effects of lithium treatment on five patients with this disease. With lithium levels maintained between 0.5 and 1.0 meq/liter, these patients showed no change in the fluctuations of their neutrophil counts. We conclude that lithium carbonate is not a simple cure for human cyclic hematopoiesis.

CYCLIC HEMATOPOIESIS (CH) is a rare disease in man; there is a closely analogous disease in grey collie dogs.1-3 In both the human disease and the animal disorder, cycling of neutrophil, monocyte, lymphocyte, reticulocyte, and platelet counts occurs with striking regularity: the period length is 21 days in man and 12 days in the dogs.8,9 The cause of cycling has been shown to be fluctuating production of cells by the marrow in both disorders,8-10 and the stem cell level of the defect has been confirmed by bone marrow transplantation.11-14

We recently reported that oral lithium carbonate is an effective treatment for grey collies.15-16 We therefore decided to treat a group of CH patients with lithium.

MATERIALS AND METHODS

Patients

Individuals with proven cyclic hematopoiesis were recruited for this study. The diagnosis of cyclic hematopoiesis was based on blood counts performed at least 3 times per week for 6 wk, which showed 2 cycles of severe neutropenia followed by rebound neutrophilia as previously described.4 In all of these patients, the neutrophil nadir was regularly associated with fever, malaise, aphthous stomatitis, and cervical lymphadenopathy, and the periodicity of these symptoms was well established.

Blood Counts

White blood cell and platelet counts were done on EDTA-anticoagulated specimens on electronic particle counters by standard laboratory methods. White cell differential counts of 100 consecutive cells were performed by a single observer, and total neutrophil counts calculated by multiplying the total counts by the percent of segmented and band neutrophils in the differential. Reticulocyte counts were done on smears of blood incubated for 10 min with brilliant Cresyl blue stain.

Treatment Protocol

The protocol for this study was approved by the Human Subjects Review Committee of the University of Washington and by the U.S. Food and Drug Administration under IND No. 16377. Prior to

<p>| Table 1. Clinical Characteristics of Patients With Cyclic Hematopoiesis |
|--------------------------|----------------|----------------|----------------|----------------|----------------||----------------|</p>
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Period Length (Days)</th>
<th>Nadir Counts</th>
<th>Peak Counts</th>
<th>Hct/Hb</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>M.S.</td>
<td>7</td>
<td>M</td>
<td>19.5</td>
<td>0</td>
<td>700-1,600</td>
<td>35/11.5</td>
<td>Fever, malaise, aphthous stomatitis, cervical adenopathy, recurrent otitis media. Meningitis at age 4.</td>
</tr>
<tr>
<td>V.S.</td>
<td>69</td>
<td>F</td>
<td>20</td>
<td>0</td>
<td>1,200-1,700</td>
<td>40/13.4</td>
<td>Severe fever, clinical depression during neutropenia. Rare aphthous stomatitis.</td>
</tr>
<tr>
<td>B.R.</td>
<td>11</td>
<td>M</td>
<td>21.5</td>
<td>0-100</td>
<td>1,500-2,800</td>
<td>36/12.0</td>
<td>Fever, malaise, occasional mouth ulcers. Died of colonic necrosis with clostridial sepsis during neutropenic episode.</td>
</tr>
<tr>
<td>R.D.</td>
<td>12</td>
<td>M</td>
<td>20.5</td>
<td>0</td>
<td>3,000-3,800</td>
<td>/12.0</td>
<td>Fever, malaise, mouth ulcers, cervical adenopathy, otitis. Brother of patient 5.</td>
</tr>
</tbody>
</table>

*All patients with neutrophil cycles also showed cyclic fluctuation of monocyte counts.
†Period length is the average of at least four cycles for each patient.
‡Cells per microliter.
LITHIUM FOR CYCLIC HEMATOPOIESIS

Lithium treatment, patients were carefully examined for goiter and neurologic abnormalities and screened with a routine chemistry battery, thyroid function tests, and urinalysis. Lithium carbonate capsules (Eskalith®, kindly supplied by Dr. Garth K. Graham, Smith, Kline, and French Laboratories, Philadelphia, PA) were administered orally beginning at 300 mg q.d. and the dosage adjusted to maintain a serum lithium level between 0.6 and 1.0 meq/liter determined weekly or biweekly. During treatment, patients were questioned closely regarding fever or signs of infection, urine flow, neurologic symptoms, and symptoms of hypothyroidism.

Statistics

The mean daily dosage of lithium was determined by summing the number of pills reportedly taken per week and dividing by 7. The serum lithium levels were determined by flame photometry or atomic absorption spectroscopy. They were measured weekly initially and then less frequently, generally every 2-3 wk.

RESULTS

Clinical

Seven patients were enrolled for study; in five of these patients neutrophil counts were obtained sufficiently frequently to allow analysis of their response. The other two patients were quite irregular in coming in for their blood counts. The clinical characteristics and laboratory findings for these five patients were typical for patients with cyclic hematopoiesis (Table 1). The mean period length for these patients was 19.5 days to 21.5 days. Monocyte cycling was always present; peak monocyte counts occurred during the neutrophil nadirs. Cyclic variation of either reticulocytes or platelets was evident in all five patients. In four patients the disease began in early childhood; in one the onset occurred at age 60.

Blood Counts

In all five patients, cyclic fluctuations in the neutrophil counts continued despite therapy for a minimum period of 3 mo (Fig. 1). Serum lithium levels were maintained between 0.5 and 1.0 meq/liter during the treatment periods. In patient 1, more vigorous therapy was used producing a higher mean serum lithium level over a longer period of time, and still no effect on the neutrophil count fluctuations could be seen. Of interest, however, this patient, as well as the two patients who failed to continue with follow-up counts, claimed to have a remarkable improvement in sense of well-being and decreased severity of clinical symptoms during severe neutropenia while taking lithium. The other four patients had no clinical improvement while on therapy.

Toxicity

All patients noted increased urine flow during treatment. In one patient this produced sufficient difficulty that alternate causes of enuresis were considered; on discontinuation of lithium, symptoms disappeared. In patient 2, a transient severe hand tremor was noted at 2 wk, and gradually increasing difficulty with fine motor control (handwriting) over 3 mo was so distressing that she withdrew from treatment; these symptoms cleared completely after lithium was stopped. No patient had abnormalities in BUN, creatinine, or thyroid function tests. While still on lithium, patient 3 developed an

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Fig. 1. Sequential neutrophil counts on five patients prior to and during lithium therapy. Lithium was started on day 0; the dose administered per day is in the upper bar graph, while the mean serum lithium level (starting 1 wk later) is plotted in the lower bar graph in each panel.
acute abdomen during a neutropenic period and died of colonic necrosis with rupture and *Clostridium perfringens* septicemia, a syndrome well recognized as a complication of cyclic hematopoiesis.4,17

**DISCUSSION**

In this trial we have shown that lithium carbonate therapy, given at doses previously reported to cause increases in neutrophil counts in man and to abrogate cycling in dogs with CH,15-16,18 does not alter the cycling of neutrophil counts in patients with this disease. There are several possible explanations for the ineffectiveness of lithium in this clinical trial. Possibly, the lithium levels in the patients were too low. One recent report demonstrated a correlation between the dose of lithium and the degree of neutrophilia in patients on chronic lithium therapy.19 Another study, however, did not show such a correlation in small groups of subjects and suggested that dose levels above 0.55 meq/liter produced an optimal increase in neutrophil count.20 We have noted that there is considerable variation between dogs in their sensitivity to lithium. Some require doses producing serum lithium levels of only 0.6 meq/liter, while others require levels of 1.4 meq/liter to stop their cycling. Thus, higher doses might be required to treat patients effectively, although at an increased risk of lithium toxicity. Another possible explanation for the failure of lithium in these patients may relate to a difference in the intracellular concentrations of lithium in man and dogs. It is known that canine erythrocytes lack an Na-K ATPase and have high intracellular sodium concentrations instead of potassium.21 Since lithium is typically distributed in parallel with sodium, this may mean that dogs have substantially higher intracellular lithium concentrations. It is also possible that the biochemical basis of human cyclic hematopoiesis differs from that of canine cycle hematopoiesis and that only the defect in the canine form is responsive to lithium therapy.

**ACKNOWLEDGMENT**

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