Lithium Therapy of Canine Cyclic Hematopoiesis

By William P. Hammond and David C. Dale

Treatment of cyclic hematopoiesis in the grey collie dog with lithium carbonate eliminated the recurrent neutropenia and normalized the other blood cell counts. These findings suggest that human cyclic hematopoiesis may be successfully treated with lithium. The effects of lithium on the monocytes, platelets, and reticulocytes, as well as the neutrophils, suggest that lithium operates on basic regulatory mechanisms affecting the most primitive hematopoietic precursor cells.

Cyclic hematopoiesis in grey collie dogs is a disorder of hematopoietic stem cells in which there are cyclic fluctuations in the number of blood leukocytes, reticulocytes, and platelets. The blood cells cycle because of periodicity in the production of cells by the bone marrow, with a period length of 11–13 days. As a consequence of the cycling of the neutrophil counts, the dogs have recurrent infections and die prematurely. At least 50% of the dogs die from infections before they reach 3 wk of age. This canine disease is a remarkably close analog of human cyclic hematopoiesis, in which regular 21-day cycles of neutrophil, monocyte, reticulocyte, and platelet counts occur and in which the neutropenic periods are associated with recurrent infections and considerable morbidity.

Lithium carbonate has been known to cause an increase in the blood leukocyte counts in man for over 25 yr. Blood neutrophil turnover and marrow neutrophil reserve studies have shown that Li+ increases neutrophil production, and in vitro studies have shown an increased growth of human granulocytic progenitor cells during lithium therapy. The mechanism by which lithium alters neutrophil production is not known, although lithium has been reported to cause an increase in colony-stimulating factor, a putative granulopoeitic substance.

Lithium’s stimulatory effect on neutrophil production in mice and man extends to the dog as well. We have therefore given oral lithium carbonate to four grey collies and examined its effect on their cyclic hematopoiesis.

MATERIALS AND METHODS

Daily blood specimens were drawn between 7:30 and 8:30 a.m. from the cephalic veins of unanesthetized dogs. Blood counts performed included total and differential white cells, platelets, reticulocytes, and packed cell volumes by standard laboratory methods. Bone marrow aspirates were performed under thiamylal (Surital, Parke-Davis) anesthesia, 15-20 mg/kg, and 500 cell differential counts reported for Wright-Giemsa stained smears of marrow spicules.

Lithium carbonate tablets were given orally to 4 dogs twice daily, initially at 150 mg, then at 300 mg/dose. Serum lithium levels were determined by routine flame photometry and were maintained between 0.5 and 1.8 meq/liter by adjustment of the lithium dosage. While on lithium therapy, the blood and marrow studies were repeated.

RESULTS

Lithium treatment produced a remarkable change in all the blood cell counts. The regular 12-day cycles of neutropenia ceased; the neutrophil counts became more stable and did not fall below 1500 cells/μl again until lithium was discontinued (Fig. 1). In one dog (064) we documented cyclic hematopoiesis for 8 cycles, demonstrated that daily endotoxin injections indeed eliminated the cycles for an equivalent period, as previously reported, and then observed the lithium effect. The prominent cycles of monocyte and platelet counts also were lost, and these counts stabilized within the normal ranges (Fig. 2). Of particular note, the hematocrits increased dramatically from a mean of 31 to a mean of 42 (Figs. 1 and 2) and, as illustrated most clearly in Fig. 1, the periodic reticulocytosis was...
mitotic neutrophil pool, similar damping of the wide swings seen in cycling grey collies was effected by lithium treatment (Fig. 3).

Associated with these changes in blood counts, the dogs no longer developed fever or clinical signs of infections and they became more active and playful.

DISCUSSION

Prior studies have shown that canine cyclic hematopoiesis is due to a periodic decrease in cell production and that this defect can be corrected by bone marrow transplantation\textsuperscript{16 - 18} or chronic endotoxin treatment (Fig. 1).\textsuperscript{19, 20} The bone marrow transplant corrects all of the hematopoietic defects, and cell counts are stabilized in the normal range.\textsuperscript{16 - 18} On the other hand, endotoxin treatment corrects the cycling of neutrophils but leaves the dogs with significant anemia and hepatic abnormalities.\textsuperscript{19, 20} Many therapies have been tried for human cyclic hematopoiesis.\textsuperscript{5 - 6} Recently, one case was treated successfully with glucocorticosteroids, but this case may be unique since other patients have not responded similarly.\textsuperscript{21} Bone marrow transplantation and endotoxin treatment, as used in the dogs, have not been regarded as suitable for the treatment of human cyclic hematopoiesis because of their potential toxicities. For this reason, we have examined lithium's effect on canine cyclic hematopoiesis prior to initiating trials in patients. Our results with lithium carbonate therapy in dogs suggest that

Fig. 2. Blood cell counts from representative 50-day period before and during lithium therapy in grey collie 032. Hematocrit is plotted as solid line, reticulocyte counts as dashed line. Cycles of monocyte and platelet counts are markedly altered.

abrogated. When lithium was discontinued, cycling of all cell types returned (Fig. 1).

In the lithium-treated dogs the characteristic marked swings in bone marrow differential counts were no longer present, and at least some mature neutrophilic cells were seen at all times. The marrow postmitotic neutrophils varied from 23% to 52% of the differential count as compared to fluctuations from 1.4% to 47% in cycling dogs (Fig. 3). For the marrow

Fig. 3. Blood neutrophil counts and bone marrow mitotic and postmitotic neutrophil pools (represented as percent of the differential count) in grey collie 032 prior to and during lithium treatment are plotted for representative 12-day periods.
this drug may be an effective and safe therapy for the human disease.

Previous studies of lithium's effect on hematopoiesis have focused on changes in neutrophil counts. The results reported here demonstrated effects on all types of blood cells. Not only did neutrophil counts stabilize, but the monocyte and platelet cycling ceased and reticulocyte variation decreased as the dog's hemato-crits returned to normal. Although it is conceivable that some of these changes could occur secondary to the increase in neutrophil counts, these data on this unique disorder suggest that lithium may have a more basic influence on the proliferation of pluripotent hematopoietic stem cells.

REFERENCES

15. Fehir KM, Rossof AH: Lithium carbonate stimulation of marrow colony forming units (CFU-c) and peripheral granulocytes in a canine model. Blood 50(Suppl 1):145, 1977 (abstr)
Lithium therapy of canine cyclic hematopoiesis

WP Hammond and DC Dale