Acta Paediatrica Hungarica, 24 (3), pp 211–216 (1983)

Effect of lithium carbonate on the bone marrow of patients treated for haematological malignancies

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Patients suffering from haematological malignancies were treated with Li_2CO_3 in order to investigate its effect on the bone marrow depleted by cytotoxic therapy. The results revealed that lithium induced a great number of cells, especially myeloids, in the previously hypoplastic bone marrow. There was a close relationship between the cellularity of the bone marrow and the changes in peripheral WBC and granulocyte counts during lithium carbonate treatment.

Leukocytosis and neutrophile granulocytosis are well known side effects of lithium carbonate which is used in the treatment of various psychiatric disorders [14, 20]. Several authors have tried to make use of these effects of lithium in adults suffering from solid tumours, in order to reduce the duration and mitigate the degree of leukopenia and granulocytopenia caused by cytotoxic agents, and thus to reduce the severity and the rate of occurrence of infections [4, 5, 12]. Similar attempts have been made in children treated for solid tumours [19]. In these instances, however, the bone marrow is rarely involved in contrast to haematological malignancies, in which it appears more reasonable to administer lithium for alleviation of the severity and duration of granulocytopenia either during induction of remission as Stein et al. [18] reported in adults treated for acute myelogenous leukaemia, or in any other phase of treatment.

In view of the regenerative capacity of the bone marrow culture under normal conditions [10, 17, 21], and after incubation with cytotoxic drugs [3] in response to lithium, it appeared interesting to explore its usefulness in clinical study. So far no studies performed in children have been reported.

Materials and Methods

Thirteen patients, ten boys and three girls, with acute lymphoblastic leukaemia had been treated with lithium carbonate [13], then bone marrow biopsy was performed as part of the regular half-yearly control. All the patients were in remission and treated according to the protocol of the Hungarian Leukaemia Study Group for Children [15], which is similar to the BFM protocol developed by Riehm et al [16].

Further four patients with ALL had been treated with Li_2CO_3 during the last two weeks of their therapy for induction of remission, and then bone marrow biopsy was done. Bone marrow reserves of two patients with highly malignant non-Hodgkin lymphoma were also investigated. They were treated according to the maintenance part of the therapeutic protocol of Wollner et al [22]. Both these patients were in remission but bone marrow suppression developed under the effect of the vigorous cytotoxic treatment. The biopsy was done immediately before and after lithium carbonate treatment.

Lithium carbonate was administered orally in a single dose of 700 mg/m² daily for two weeks while cytotoxic therapy was left unchanged. Quantitative and qualitative changes of peripheral white blood cells were recorded, and the serum lithium levels were also determined. 500 leukocytes were counted for differentials. The cellularity of the bone marrow, the ratio of erythroids and myeloids, and the maturation of different cell lines were examined in bone marrow specimens taken by Yamshidi needle.

For statistical analysis Student's *t*-test was used. The results were compared to baseline data measured at the beginning of lithium treatment, or with controls. Control cases receiving the same cytotoxic therapy were chosen by randomization.

Results

Two groups could be distinguished on the basis of bone marrow cellularity (Fig. 1). The first group was characterised by a normal myeloid-erythroid ratio in the bone marrow ($M/E > 2.5$), and the second one showed erythroid hyperplasia ($M/E < 0.5$). Hypercellularity and a distinct myeloid predominance developed in the bone marrow only in patients treated with lithium. The cellularity of the bone marrow of controls of the first group was normal with a slight myloid predominance. In the 2nd and 4th weeks there was a significant difference in peripheral WBC count between patients treated with Li_2CO_3

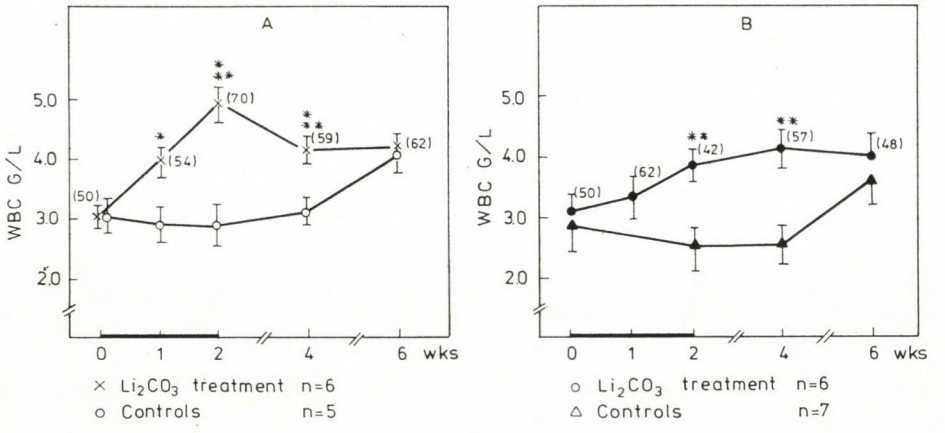


Fig. 1. Effect of Li_2CO_3 treatment (heavy line) on WBC count in patients with normal myeloid-erythroid ratio (A) or with erythroid hyperplasia (B) in the bone marrow ($\bar{x} \pm SE$). Number in brackets, granulocyte ratio in blood. * $p < 0.05$ in comparison to baseline data, ** $p < 0.05$ in comparison to controls

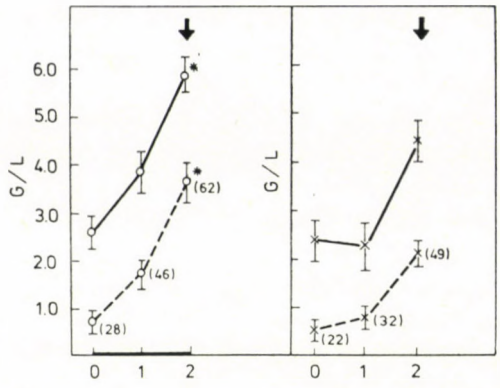


FIG. 2. Effect of Li_2CO_3 treatment (heavy line) on WBC (thin line) and granulocyte (broken line) count in the last two weeks of remission induction of ALL ($\bar{x} \pm SE$). Dots, patients treated with Li_2CO_3; crosses, controls. Number in brackets, granulocyte ratio in blood. Arrow, bone marrow biopsy. * $p < 0.05$ in comparison to controls

and controls. Significant differences from baseline data were observed not only in the peripheral WBC counts but in the absolute granulocyte counts as well.

Lithium was effective but to a much less extent when bone marrow was normocellular with erythroid predominance. In these cases differences were significant in the 2nd and 4th week in respect of leukocyte and absolute granulocyte counts in comparison with controls whose bone marrow was dominated by erythroid hyperplasia ($M/E < 0.5$), but not in comparison with baseline data.

Lithium carbonate administered during induction of remission (Fig. 2) significantly increased the number of WBC and absolute granulocytes by the end of the treatment. An increase in the granulocyte ratio was also seen.

Cytomorphologic analysis of the bone marrow specimen taken at the end of induction of remission showed that the cellularity of the bone marrow and the predominance of myeloid cells in the patients treated with lithium carbonate significantly exceeded that of controls (Figs 3 and 4). Histological analysis of the bone marrow depleted by cytotoxic drugs revealed that Li_2CO_3 induced a great number of cells in the previously hypoplastic tissue (Figs 5 and 6). Especially the production of myeloids had been stimulated restoring the normal myeloid-erythroid ratio. This striking effect of lithium carbonate was reflected by a distinct leukocytosis in peripheral blood.

DISCUSSION

Examination of bone marrow is a more reliable index of the effect of lithium than are the quantitative and qualitative changes of white blood cells in peripheral blood. There are strict indications for bone marrow examination, and we used this oppor-

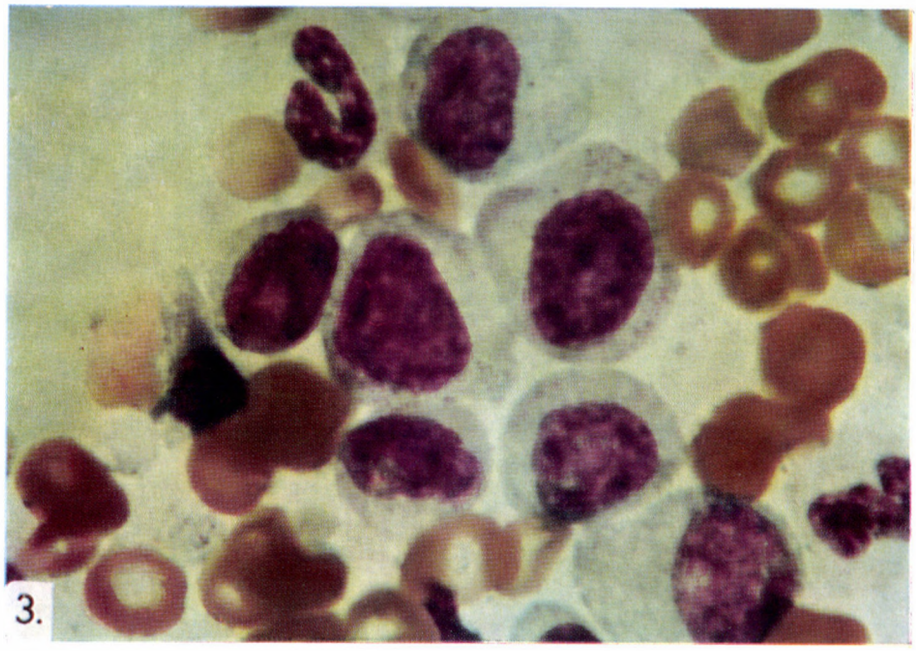
tunity to compare the effect of the drug on bone marrow and peripheral blood.

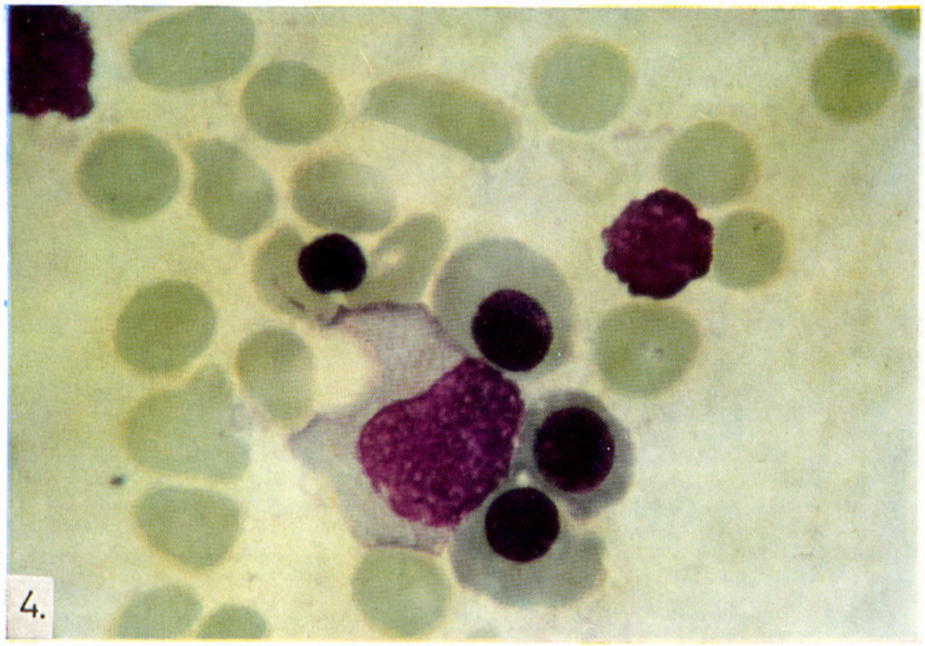
Our observations suggest that lithium carbonate administered during induction of remission enhances the cellularity of the bone marrow and increases the peripheral leukocyte and granulocyte count. Gallicchio et al. [7] observed the same increase in bone marrow in lithium treated mice. The myeloid predominance in the bone marrow and the granulocyte ratio in peripheral blood seem to have increased simultaneously, thus there is a close relationship between the bone marrow cellularity and the changes in peripheral WBC and granulocyte counts during lithium treatment. In the case of a normal bone marrow cellularity, a sudden increase in WBC and a sharp and lasting increase in the peripheral granulocyte count could be observed (early reaction). A less marked and delayed leukocytosis and granulocytosis developed when the bone marrow was hypocellular and contained only few myeloids (delayed reaction). The bone marrow reserve capacity and its mobilization were normal in patients with clinical expression of bone marrow depression.

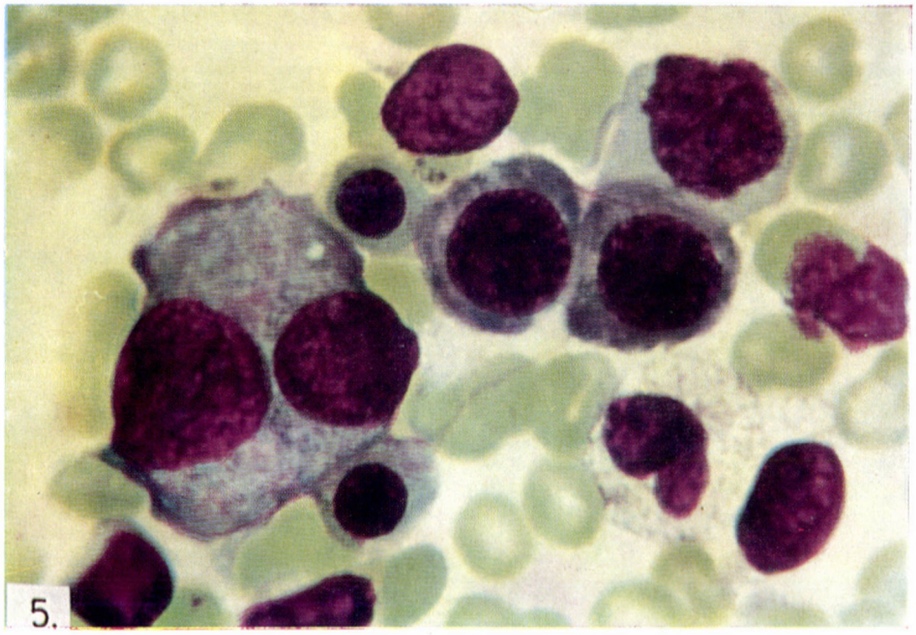
There are several possibilities to explain the present results. Lithium seems to have different effects on haematopoiesis, thus on the increase in the number of cells in the bone marrow and in peripheral blood. Lithium, added to normal bone marrow cells cultured in vitro, stimulated the growth of granulocytic colonies [17], increased the number of granulocyte progenitor cells [11], and the number of granulocyte/macrophage colony forming units (CFU-GM) [20], but only in the presence of colony stimulating activity (CSA) [8, 10, 11]. Lithium enhances the production of CSA [10] especially by peripheral mononuclear cells [21]. Lithium is able to induce cells that are normally quiescent and non-cycling [8].

The site of action of lithium on the bone marrow is not clear. Lithium may act at the level of granulocyte progenitor cells and directly stimulate the proliferation of pluripotential stem cells, as has been shown in cell cultures [11] and in mice [7]. Lithium stimulates the mononuclears to produce a humoural pluripoietin-analogous substance, and thus it may induce pluripotent stem cells to differentiate into various cell lines [11]. Fernandez and MacSween [6] found that lithium decreased the number of T-cell colonies, so they assumed that it would affect the even more immature totipotent stem cells as well. This suggests that lithium may be useful in the treatment of different disorders supposed to be due to a deficiency of pluripotent stem cells [1, 2, 9].

Since in studies in vitro no close correlation could be found between the lithium concentration in the medium and the stimulatory effect, some indirect mechanism appears to be more likely than a direct one. There are several factors influencing the actual condition and the reaction of the bone marrow to lithium, especially under circumstances in vivo.







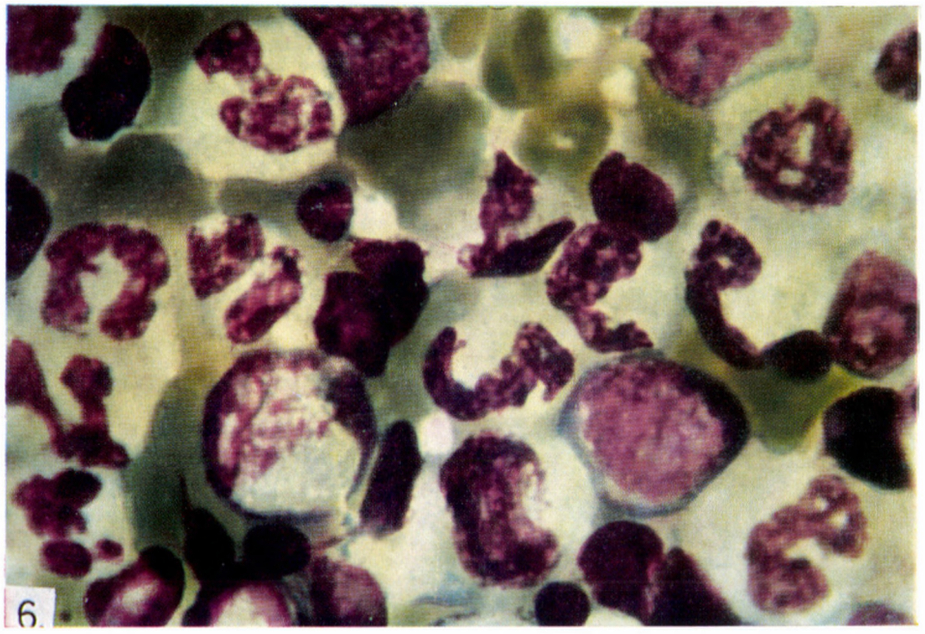


FIG. 3. Bone marrow at the end of induction of remission after lithium treatment. Bone marrow biopsy, imprint preparation, May–Grünwald–Giemsa staining, ×1000

FIG. 4. Bone marrow at the end of induction of remission, control. Bone marrow biopsy, imprint preparation, May–Grünwald-Giemsa staining, ×1000

FIGS 5–6. Effect of Li_2CO_3 on bone marrow depleted by cytotoxic drugs. Before treatment hypocellularity and erythroid hyperplasia (Fig. 5), after treatment hypercellularity and myeloid predominance (Fig. 6). Bone marrow biopsy, imprint preparation, May–Grünwald–Giemsa staining, ×1000

Thus, nutritional status, hepatic and renal function, the presence or absence of infection and especially the reserve capacity of the bone marrow and a cytotoxic therapy may modify the reaction [19]. It has to be emphasized that if there is a reasonable reserve of marrow stem cells, lithium may induce a transient or sustained increase in their production [11]. The same has been shown by Casirola et al [4] in that if there was only a little stem cell pool in the marrow the granulopoiesis induced by lithium was poor.

Bone marrow can be sampled only under strict indications, and so the reserve capacity cannot be examined often. For this reason, every observation referring to the actual condition of the bone marrow may be important. Our observations were made in a small number of patients, but the results indicate that a short term lithium treatment may be useful for estimation of the actual condition and of the reserve capacity of the bone marrow. As the clinical signs of its exhaustion and inhibition are the same, a lithium-test may help to differentiate and to decide upon adequate therapy.

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Received 20 November 1982

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