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Effect of lithium carbonate on the peripheral leukocyte count in children suffering from haematological malignancies

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Effects of lithium carbonate on peripheral white blood cell and granulocyte counts were investigated in children treated for acute lymphoblastic leukaemia and non-Hodgkin malignant lymphoma. Li_2CO_3 given orally for two weeks in a single daily dose of 700 mg/m² caused a significant and lasting increase in the peripheral WBC and granulocyte counts and increased the granulocyte ratio during induction of remission and maintenance cytotoxic therapy. Haematologic actions and the long-term effect of lithium carbonate are discussed.

Leukocytosis and neutrophil granulocytosis was reported to develop in patients treated with Li_2CO_3 for manic-depressive psychosis [12, 20]. Later lithium has been found effective in reducing the degree and duration of neutropenia in adults receiving chemotherapy for small-cell carcinoma of the lung [11], carcinoma of the prostate [3], Hodgkin and non-Hodgkin malignant lymphoma [2], acute myeloid leukaemia [17], and in children with solid tumours [19].

Since the effects of lithium carbonate in adults suffering from lymphoblastic leukaemia are contradictory [1, 2] and no examinations were performed in children, the present study was designed to explore the effects of lithium carbonate as supportive treatment in children suffering from acute lymphoblastic leukaemia.

Materials and Methods

Twenty-one children, 16 boys and 5 girls, were treated with Li_2CO_3; 15 patients suffered from acute lymphoblastic leukaemia (ALL) and 6 patients from highly malignant non-Hodgkin lymphoma (T-lymphoblastoma, nHml). All were in remission, and were investigated during maintenance cytotoxic chemotherapy, either according to the therapeutic protocol of the Hungarian Leukaemia Study Group for Children, which is highly similar to the BFM protocol developed by Riehm et al [13], or according to the protocol of Wollner et al [21]. Another 4 patients were treated during the last two weeks of induction of remission of ALL. Li_2CO_3 was given in a single daily dose of 700 mg/m² orally for two weeks and the cytotoxic therapy was not interrupted. During maintenance therapy prednisone pulse treatment had been terminated at least two weeks before Li_2CO_3 was given. During induction of remission prednisone treatment was continued.

Quantitative and qualitative changes in peripheral white blood cells (WBC) and serum lithium levels were measured. Five hundred leukocytes were counted for the differentials. Serum lithium levels were determined by atomic absorption method.

The results were compared either with baseline data, measured at the beginning of the lithium treatment or with controls. Controls receiving identical cytotoxic treatment were collected in a randomized fashion. Results were compared with another lithium study where 400 mg/m² of Li_2CO_3 was given. Since WBC counts and differentials in patients with ALL and nHml were not statistically different, the two groups were combined for evaluation.

Statistical analysis was done with Student's t test.

Results

Serum lithium concentrations of our patients (0.72 ± 0.07 mmol/l and 0.56 ± 0.06 mmol/l in the 1st and 2nd weeks respectively) reached therapeutic levels (>0.55 mmol/l) [18], but remained below the toxic concentration (>1.5 mmol/l) [18, 19]. When only 400 mg/m² of lithium carbonate was given, the therapeutic range could hardly be reached. As it can be seen in Fig. 1, in both groups there was a considerable decline of the serum lithium level within a week.

Lithium carbonate, given during the last two weeks of remission induction therapy, caused a significant increase in the number of peripheral WBC; a rise in the absolute number and ratio of the circulating granulocytes at the end of the lithium therapy was also observed (Fig. 2).

During maintenance chemotherapy, 700 mg/m² of lithium carbonate caused a significant and lasting increase in the number of peripheral WBC (Fig. 3). The differences were significant at the end of the 1st and 2nd weeks in comparison to controls and baseline data.

Investigation of the peripheral WBC and absolute granulocyte counts showed that the increase and duration of granulocytosis was as high and lasting as that of the WBC (Fig. 4). The changes of the granulocyte ratio showed that the granulocytosis induced by lithium may have been responsible for the leukocytosis.

Four patients suffered from viral infection and were compared to con-

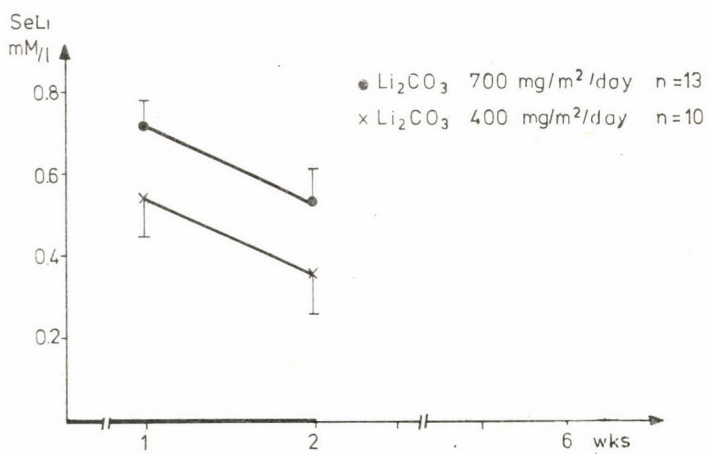

Fig. 1. Serum lithium level ($\bar{x}$ ± SE) in patients treated with Li_2CO_3 for two weeks (full line)

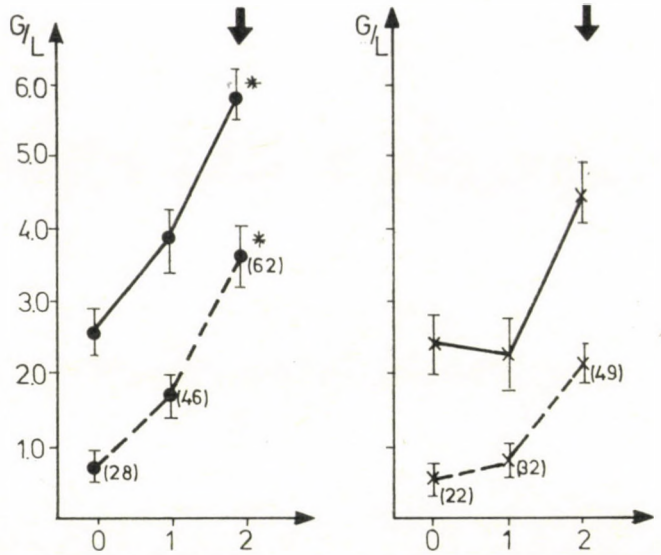

FIG. 2. Effect of Li_2CO_3 treatment (thick line) on WBC (full line) and granulocyte (broken line) counts in the last two weeks of induction of remission of ALL ($\bar{x} \pm SE$); dots, patients treated with Li_2CO_3; crosses, controls; arrow, bone marrow biopsy; * $p < 0.05$ in comparison to controls and to baseline data. Number in brackets represents the granulocyte ratio in per cent

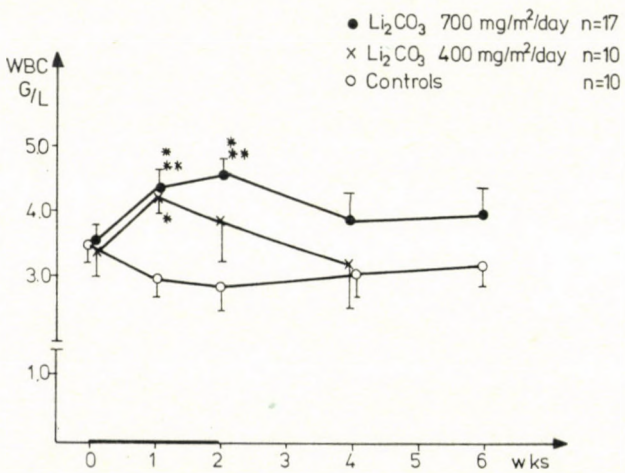

FIG. 3. Effect of Li_2CO_3 treatment (full line) on WBC count ($\bar{x} \pm SE$). * $p < 0.05$ in comparison to controls; ** $p < 0.05$ in comparison to baseline data

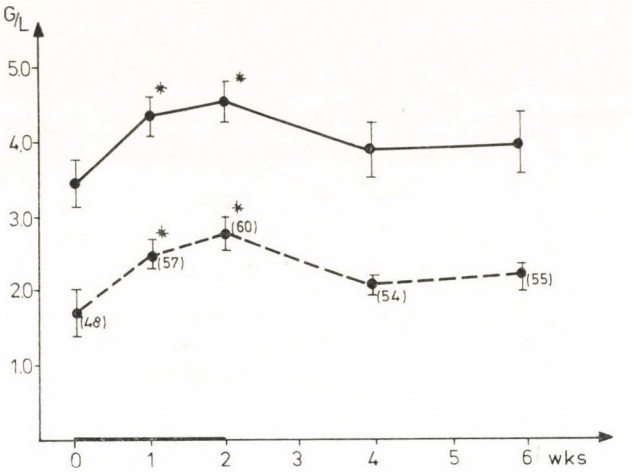

FIG. 4. Effect of Li_2CO_3 treatment (thick line) on WBC (full line) and granulocyte counts (broken line) ($\bar{x} \pm SE$). * $p < 0.05$ in comparison to baseline data. Number in brackets represents the granulocyte ratio in per cent

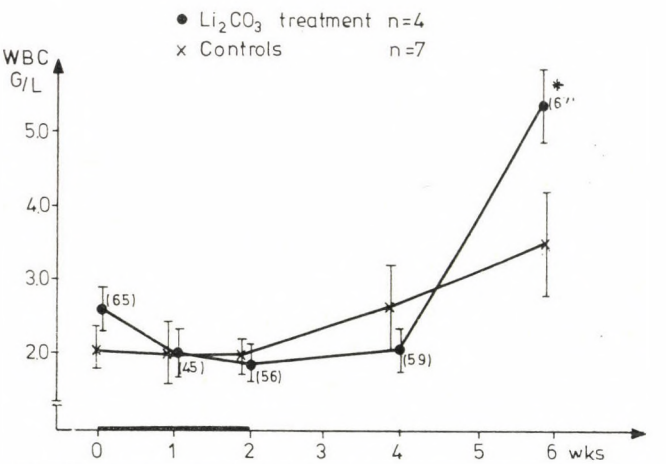

FIG. 5. Effect of Li_2CO_3 treatment (full line) on WBC counts during infection ($\bar{x} \pm SD$). * $p < 0.05$ in comparison to controls and to previous data. Number in brackets represents the granulocyte ratio in per cent

trols with similar symptoms. The cytotoxic treatment remained unchanged in both groups. Lithium treatment did not cause an early response, but after the 4th week there was a significant increase in the number of WBC in the group treated with lithium (Fig. 5). The changes in the granulocyte ratio seemed to be similar.

DISCUSSION

In the present study lithium induced a significant degree of leukocytosis and granulocytosis at the end of treatment during induction of remission. The increase in the proportion of granulocytes was particularly evident. This was in agreement with the ob-

servations of Bandini et al [1] who showed that in adults lithium may shorten the duration and mitigate the severity of neutropenia during induction of remission of ALL. Casirola et al [2] however, could not confirm these observations.

Lithium carbonate in a daily dose of 700 mg/m^2 produced a significant leukocytosis in the 1st and 2nd weeks with a lasting cell production during maintenance cytotoxic therapy. Various doses of lithium carbonate resulted in different serum lithium levels as well as in different degrees of leukocytosis. Stein et al [18] found that a significant degree of leukocytosis could be produced only when the serum lithium concentration exceeded 0.55 mmol/l. Such a serum lithium concentration could only be produced when a lithium carbonate dose of 700 mg/m^2/day had been administered. In children with solid tumours 400—600 mg/m^2/day was followed by therapeutic lithium levels and a definite increase of the WBC count [19]. The differences may be explained by the lasting suppression of the bone marrow of patients with haematologic malignancies. The correlation between the administered dose of lithium carbonate, the serum lithium level and granulocyte production is not linear [14, 18] but may be close to it. It has been shown that the higher the serum lithium level, the longer the elimination half-time, and the greater the effect (Minsker et al cit. 7). This relationship has been supported by experiments performed in mice [6].

The administered dose of lithium carbonate appears to be important [6, 18]. If the serum lithium concentration exceeds 1.5 mmol/l, in addition to a rebound leukopenia, one has to reckon with an increased risk of lithium toxicity. It has been suggested that the reduced mature leukocyte reserve in the bone marrow resulting from the release of leukocytes facilitates the toxic effect of lithium carbonate on the bone marrow [6].

During lithium treatment the absolute granulocyte count increased significantly in the 1st and 2nd weeks. The increase of the granulocyte ratio in the differentials was lasting and considerable. As to the mechanism of these responses to lithium carbonate, a direct stimulation of granulocyte colonies, enhanced colony stimulating activity (CSA), proliferation of the granulocyte progenic cells and the pluripotential stem cells are the most reasonable alternatives [4, 5, 8, 9, 10, 14].

The changes in the serum lithium levels and the long-term effect of lithium carbonate could be explained by its turnover within the organism, and by the dynamics of its elimination. The drug is distributed in the whole body water, but crosses cell membranes at a slow rate. This accounts for the delayed (6–10 days) therapeutic response, and the slow (2 3 weeks) elimination rate [7, 15]. Cytotoxic therapy by affecting cellular metabolism may alter the distribution and excretion rate of lithium.

It should be emphasized that lithium therapy is ineffective in infections, but after its elimination a re-

bound leukocytosis develops. This is probably due to the facilitatory effect of lithium on the deliberation reaction [16] of the bone marrow after repression.

In conclusion it can be said that in children treated for ALL or non-Hodgkin malignant lymphoma lithium carbonate in a daily dose of 700 mg/m^2 administered for two weeks is capable to induce a lasting and significant leukocytosis and granulocytosis during remission induction and maintenance cytotoxic chemotherapy.

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