THE USE OF URETHANE (ETHYL CARBAMATE) IN THE TREATMENT OF LEUKEMIA

A Preliminary Report

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HADDOW and Sexton\textsuperscript{1} noted a coincidental depression of the leukocyte count during the course of observations on the effect of various forms of urethane on the growth of experimentally produced tumors in the rat. As a result, the various forms of urethane, principally ethyl carbamate, were subsequently utilized in the treatment of leukemias and other types of malignant disease by Paterson, Thomas, Haddow and Watkinson.\textsuperscript{2} Encouraging results followed the administration of urethane in the majority of 13 cases of myelogenous leukemia and, to a lesser extent, in 9 cases of lymphatic leukemia. The most favorable response consisted of a reduction of the total leukocyte count to normal levels, production of a more nearly normal differential pattern, elevation of hemoglobin levels and diminution in the size of enlarged lymph nodes or spleen. These effects were sustained for variable periods, the longest period of observation recorded being eleven months. Symptoms of gastrointestinal irritation of mild to moderate degree rather commonly followed administration of the drug. Aplastic anemia developed in 2 cases, in one of which there was a fatal termination. In general, the results obtained were regarded as much like those following the use of the standard method of irradiation therapy.

The mode of action of urethane remains obscure. Kirschbaum and Lu\textsuperscript{3} observed that the administration of a single anesthetic dose of urethane to mice with myelogenous leukemia resulted in a drop, within twenty-four hours, in the total leukocyte count and in the appearance of many mature cells in the bone marrow. The number of mitotic figures in the myeloid cells of the marrow was decreased and it was suggested that maturation may have been secondary to inhibition of mitosis in blast cells. Johnson\textsuperscript{4} observed that urethane exerts an antisyufnalamide effect, similar to that of para-aminobenzoic acid, in work with certain strains of luminous bacteria. This would suggest that urethane's growth-inhibiting property may result from interference with utilization, in cellular metabolism, of some natural amine.

At the Mayo Clinic, clinical experience with urethane (ethyl carbamate) in the treatment of leukemic states now covers a period of approximately eight months. While the ultimate evaluation of this substance as a means of treatment for the leukemias obviously remains to be determined in the future, certain current observations may be of interest to those concerned in the management of these perplexing conditions.

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URETHANE IN TREATMENT OF LEUKEMIA

RESULTS OF TREATMENT

Chronic myelogenous leukemia. In 14 cases, urethane is now being used as the sole means of treatment. The patients in these cases have been under treatment for periods ranging from seven weeks to eight months. In all instances, the response to treatment thus far has been regarded as satisfactory and no supplementary measures have been required. There has been a consistent reduction in the total leukocyte count (table 1) accompanied by a parallel reduction in the degree of myeloid immaturity apparent in differential analysis of smears of the peripheral blood and sternal bone marrow. The erythrocyte count and hemoglobin values have either shown a significant increase or have remained virtually unchanged. In no instance has anemia or clinically significant thrombocytopenia developed during the course of treatment. Splenomegaly has been consistently and rapidly diminished in degree, although in no case has a previously palpable spleen disappeared entirely. The degree of response apparently was not affected by the initial level of the total leukocyte count, the duration of the illness or the amount of previous irradiation therapy.

A satisfactory response to treatment was achieved in three to ten weeks (average six weeks) following the administration of 21 to 168 Gm. of urethane (average 80 Gm.). The drug was usually administered in a dosage of 1 Gm. three times a day at the outset. This amount was reduced to 1 to 2 Gm. daily as the leukocyte count descended. The primary fall in the leukocyte count usually occurred seven to fourteen days after the institution of therapy and was often preceded by a transient elevation. However, in 2 cases, twenty-one to twenty-eight days of treatment was required to produce the initial depression of the leukocyte count.

The dosage necessary to maintain the leukocyte count at relatively normal
levels (less than 20,000 per cu. mm. of blood) has been highly variable, although for the 2 patients under observation for the longest periods, 0.5 to 1.0 Gm. daily has been found adequate. Weekly leukocyte counts are necessary in determining the long-term needs in the individual case, the amount of urethane administered being increased or reduced accordingly. An effort has been made to maintain the total leukocyte count at 20,000 or less per cu. mm. and the drug has been temporarily discontinued when the total leukocyte count has been less than 10,000 per cu. mm. No cases of chronic leukopenic myelogenous leukemia were included in this series.

On cessation of therapy, recurrence of leukocytosis with myeloid immaturity invariably occurred after variable periods of time.

Mildly to moderately severe symptoms of gastrointestinal irritation occurred in approximately one third of the cases but disappeared with continued administration of the drug, although a reduction in dosage was sometimes necessary. A direct relationship between the size of the daily dose and the frequency of gastrointestinal complaints was soon established and, in recent months, an amount in excess of 3 Gm. daily has rarely been prescribed. No other toxic manifestations attributable to the drug were observed in this series.

Acute myelogenous leukemia. Urethane was administered in 2 cases for periods of ten to fourteen days with no significant change in the clinical course, although there was some decrease in the degree of myeloid immaturity in smears of the peripheral blood and sternal marrow.

Chronic lymphatic leukemia. The drug was administered, in apparently insufficient amounts, in 2 cases. There was no appreciable effect on the total leukocyte count.

Acute lymphatic leukemia. Urethane has been administered for periods of one to three weeks in 8 cases. In three instances, there was a precipitous fall in the total leukocyte count, but in none was the general clinical course materially influenced.

Acute monocytic leukemia. In 2 cases, treatment of one to three weeks' duration produced no measurable hematologic or clinical change.

Comment

Our experience would indicate that urethane can be expected to produce a temporary hematologic remission in cases of chronic myelogenous leukemia. This remission is similar, in superficial characteristics, to that observed after irradiation therapy. There is, at the present time, no indication that urethane offers more than other agents which are used palliatively in this disease. However, by virtue of its convenience of administration and the possible advantage of controlled, continuous action, urethane may be found preferable to other methods of treatment in use at the present time.

We have had insufficient experience with the use of urethane in the treatment of chronic lymphatic leukemia to warrant an opinion as to its efficacy. However, the reported experiences of Paterson and co-workers would seem to justify continued use of the substance in such cases.

While, like irradiation therapy, urethane may produce a rapid decrease in the number of immature leukocytes circulating in the blood in some cases of acute
myelogenous and lymphatic leukemia, there is no evidence to suggest that the usual course of these conditions has been beneficially influenced.

Despite the absence of serious toxic effects encountered in this series to date, the potential production of aplastic anemia and other complications by this substance must be kept in mind.

SUMMARY

Limited experience with the use of urethane in the treatment of leukemia indicates that this substance presents a considerable promise as a palliative agent in chronic myelogenous leukemia. It has no apparent value in the treatment of acute leukemia.

Further extensive observation will be necessary to provide a true measure of the clinical usefulness of this preparation.

REFERENCES

THE USE OF URETHANE (ETHYL CARBAMATE) IN THE TREATMENT OF LEUKEMIA: A PRELIMINARY REPORT

CHARLES H. WATKINS, TALBERT COOPER and HERBERT Z. GIFFIN