Blood Urethane Levels Achieved with Entero-Coated Tablets.* (18135)

MARTIN C. ROSENTHAL AND RICHARD H. SAUNDERS, JR.†
(Introduced by Mario Stefanini.)

From the Ziskind Laboratories (Hematology Section), Joseph H. Pratt and New England Center Hospitals and the Department of Medicine, Tufts College Medical School, Boston, Mass.

The discovery of the growth suppressive power of the carbamic esters has raised this long known chemical group to the status of chemotherapeutic agents. Their failure to influence favorably advanced cases of malignant diseases in man has been more than compensated for by the discovery of their inhibitory action on white cell neoplasia. Peterson, Thomas, Haddow and Watkinson(1) first treated leukemias with ethyl carbamate (urethane). Since then, numerous articles have appeared in the literature dealing with the therapeutic results of this drug. In general, it appears to be more effective in chronic leukemias than in acute leukemia. More recently, Loge and Rundles(2) have called attention to the clinical effectiveness of urethane in the treatment of multiple myeloma.

Regulation of the dosage of urethane is difficult at times especially when the white count is normal or decreased. In leukemic states associated with high white cell count no such difficulty is encountered; the white blood cell count acting as a sensitive indicator. In these cases, a rapidly falling total white count or leucopenia calls for diminution or cessation of therapy. The inverse relationship between white count and dosage permits excellent control, (Fig. 1), and protects against the dangers of severe hepatic damage or aplasia of the bone marrow.

The utilization of urethane blood levels as a guide to dosage schedules suggested itself

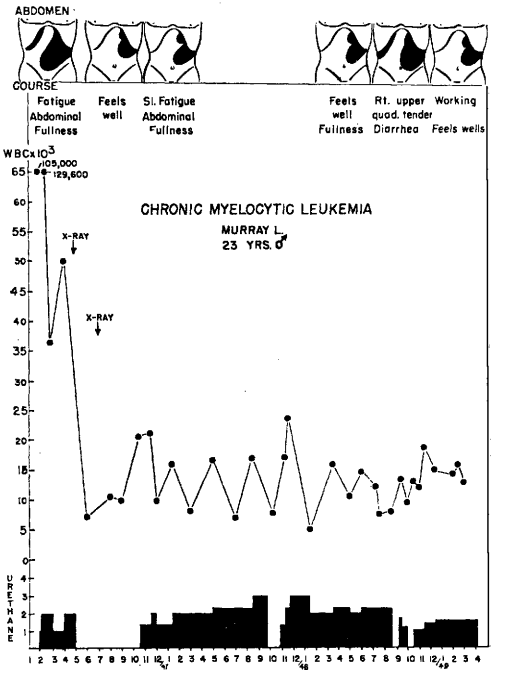

FIG. 1.

in those cases in which the white count offered no reliable guide. However, the very simplicity of the urethane molecule makes its quantitative estimation difficult. Archer, Chapman, Rhoden and Warren(3) have utilized the ethyl group as an aid in the measurement of the blood urethane level. The process consists essentially of alkaline hydrolysis of urethane to ethanol, carbon dioxide and water, the distillation and recovery of the ethanol and its quantitative measurement. This bears a direct relationship to the amount of urethane being estimated, which can then be calculated. These authors recnogized that other volatile reducing substances may be formed during hydrolysis and

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1. Paterson, E., Apthomas, I., Haddow, A. and Watkinson, J. M., *Lancet,* 1946, v200, 677.

2. Loge, J. P., Rundles, R. W., *Blood,* 1949, v4, 202.

3. Archer, H. E., Chapman, L., Rhoden, E. and Warren, F., *Biochem. J.,* 1948, v42, 58.

performed blank determinations on samples in each case. Values cited were of 22 mg of urethane per 100 cc following a dosage of 3 g daily for 14 days and of 10 mg per 100 cc following 1 g daily for 50 days. The ingestion of 2 g in one dose resulted in a 28 mg% rise.

In the present study, an attempt was made to evaluate the relationship between dosage of drug and the blood urethane level in 10 patients all of which were under treatment for leukemia or multiple myeloma, using the method of Archer *et al.*(3). All patients had been on urethane therapy two weeks or longer. No effort was made to secure samples at set hours after the ingestion of the urethane tablets. However, all patients except one had samples drawn 3 to 4 hours after their usual divided maintenance dose. Urethane was administered in the form of enteric coated tablets (Lilly) 0.3 g each. The daily dosage, which ranged from 1 to 4 g was given in 3-4 divided doses usually directly after meals. Venous blood was used with heparin as an anticoagulant. A standard Folin-Wu Filtrate was made. All determinations were made on unstored samples within 2 hours after drawing the blood.

Results. Nineteen determinations were made on 10 patients. There appeared to be little correlation between the dosage schedule and the blood level obtained. For example, some patients receiving as much as 3 g of urethane daily showed either a low or even no measurable blood level (Fig. 2). In the group of patients receiving 2 g per day, blood levels ranged from 4 mg to 27 mg%. On a dosage scheduled twice this value, no higher blood levels were achieved.

Discussion. From our data it seems likely that urethane blood levels offer little aid in the guidance of therapy with this drug. Some cases having either no appreciable or very low urethane blood levels displayed well defined clinical improvement with or without leucocytic depression, testifying that the drug was being absorbed. More recently, using a more specific method for urethane determination but

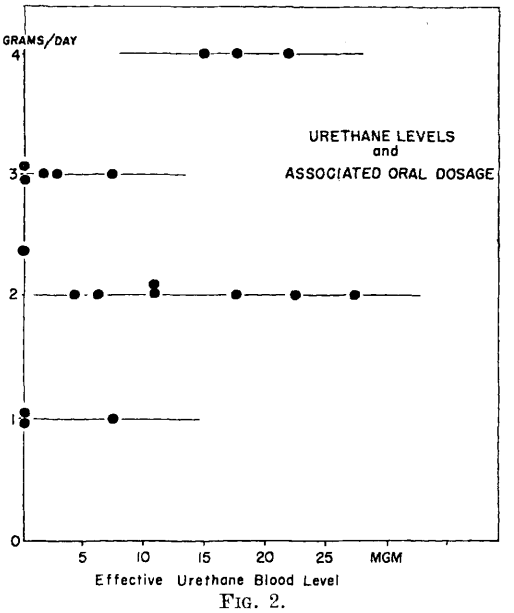

FIG. 2.

based on the same general principle(4), a similar lack of correlation was found in a limited number of determinations. It is possible that the enteric coating on the urethane tablets altered intestinal absorption so that therapeutically active but very low (blood) levels are obtained. In addition the unpredictability of intestinal absorption and the degree of tissue utilization of the drug(5) undoubtedly affect the reliability of blood urethane values as a therapeutic guide.

Summary. Blood urethane levels using the method of Archer *et al.* were performed on patients receiving enteric-coated urethane tablets for the treatment of leukemia and multiple myeloma. Blood levels ranging from 0 to 27 mg per 100 cc of blood were obtained. The correlation between dosage of the drug, blood level and clinical response was poor. This negates the value of such determination in the regulation of oral urethane therapy.

4. Benotti, J., White, J., personal communication, 1950.

5. Progress Report on the Chemotherapy of Leukemia, Southern Research Institute, 1949.

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