Partial Reversal of the Antileukemic Activity of A-Methopterin by Cortisone*

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It has been reported that dehydroisoandrosterone in relatively large amounts is able to replace folic acid in permitting the growth of *Streptococcus faecalis* and *Lactobacillus casei* (2). In the absence of folic acid and citrovorum factor (CF), cortisone promoted the growth of *S. faecalis* and *Leuconostoc citrovorum*, respectively (1). Furthermore, cortisone reversed the growth inhibition of *L. citrovorum* produced by toxic amounts of aminopterin. This reversal was thought to be competitive, indicating that cortisone is a catalyst rather than an end-product of the enzyme reaction inhibited by aminopterin (1).

More recently it has been observed that injection of cortisone alone was ineffective in overcoming aminopterin toxicity to rats; however, injection of cortisone in the presence of limiting amounts of citrovorum factor appeared to have some protective effect (3).

That cortisone, as well as A-methopterin, will provide for temporary remissions in certain cases of acute leukemia in children is well established. These two agents are now quite often used in combination or as alternate therapy in acute leukemia.

The present note provides evidence that these compounds are not additive in their antileukemic activity against mouse leukemias L1210 or L4946; in fact, cortisone appears partially to reverse the effectiveness of A-methopterin when the two agents are administered simultaneously.

**EXPERIMENTAL**

A-methopterin consistently increases the life span of mice with L1210 or L4946 leukemia; however, cortisone does not affect significantly the survival time of mice with either of these leukemias. In an attempt to determine the effectiveness of combination therapy, A-methopterin plus cortisone was administered to DBA mice with L1210 leukemia and Akm mice was L4946 leukemia, and the survival times of the combination-treated mice were compared to those of groups receiving A-methopterin or cortisone alone. Groups of ten mice each were employed throughout these studies. In all experiments, leukemic cells were inoculated intraperitoneally, and treatment was initiated 4 hours later and continued every other day for a total of ten injections or until death.

The data summarized in Table 1 permit a comparison of the effects on the life span of leukemic mice of the combination mentioned above and the substances used individually.

Limited studies have indicated that cortisone interferes with the inhibitory effects of A-methopterin on the subcutaneous growth of leukemia L1210.

As a final check on the reproducibility and significance of these observations, a group of 100 DBA mice was given inoculations of L1210 leukemia, randomly distributed into ten groups of ten each, and treated with various levels of A-methopterin plus cortisone as well as with each agent alone. The detailed protocol of this experiment, together with survival data, are presented in Table 2.

**DISCUSSION**

The data presented suggest that cortisone not only fails to provide additive antileukemic action in mice, when used in combination with A-methopterin, but reduces the effectiveness of the latter. This effect has been consistent and is highly significant from a statistical point of view.

It cannot be assumed, in the absence of clinical reports, that the present results carry over to human leukemia; however, the correlation between responses of human and mouse leukemias to chemotherapeutic agents in the past has been good.

These in vivo results seem to follow the pattern of earlier observations on the reversal by cortisone of the toxicity of aminopterin on certain bacteria (1). From a theoretical standpoint it is of interest to consider that the antileukemic activity of an inhibitor (A-methopterin) of the synthesis of nucleic acids can be inhibited significantly by a
steroid hormone, since there is considerable evidence that nucleotide and steroid metabolism are sites of biochemical malfunction in neoplasia.

SUMMARY

Data have been presented which indicate that cortisone significantly reduces the antileukemic activity of A-methopterin in two strains of mouse leukemia.

REFERENCES


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