GUANAZOLO IN THE THERAPY OF HODGKIN’S DISEASE

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The principle of competitive inhibition as elaborated by Woolley has found wide therapeutic application in influencing enzyme reactions in animal organisms. The use of this principle has been dramatically successful with regard to chemotherapeutic agents and heavy metal poisoning. There are also numerous indications of the validity of this concept with regard to the effect of chemical substances on the mammalian organism. In 1945, Hitchings et al. produced a group of purine analogues which had the capacity to inhibit nucleic acid synthesis. Among a number of these compounds tested by Kidder it was found that a substituted purine, guanazolo (5-amino-7-hydroxy-1H-v-triazolo[d]pyrimidine), was the most powerful purine inhibitor, producing its effect by being included in the nucleoprotein.

A necessary constituent of the diet of the animal organism Tetrahymena geleii is the purine, guanine. Tetrahymena geleii, which resembles the vertebrate with regard to its amino acid and vitamin requirements, has the significant difference of being unable to synthesize guanine. The mammal can synthesize guanine from adenine but cannot utilize dietary guanine. It was shown that inhibition of growth in Tetrahymena by guanazolo was completely reversed by guanine. The basis for the inhibitory activity of guanazolo was believed to be its complete utilization by the guanine-enzyme system, with the formation of the nucleoside and nucleotide of the guanine analogue in place of those of guanine. The formation of the abnormal nucleotide would apparently be fatal in the later stages of the development of the organism. By analogy, if tumor cells were unable to synthesize guanine, unlike their mammalian host, then guanine analogues would inhibit abnormal growth without toxic effect on the host organism.

Employing transplanted mouse adenocarcinoma (Eo 771), spontaneous mammary adenocarcinoma in mice, and mice with lymphatic leukemia, Kidder et al. found that guanazolo checked tumor growth without producing death of cells with a dose of 1 mg. daily subcutaneously for five to twenty days. They believed that the effects of guanazolo were the same as with Tetrahymena.

Recently a preliminary study on the clinical toxicity of guanazolo in 8 cases of cancer resistant to radiation was reported by Armstead et al. The drug was given intravenously with an equimolar quantity of sodium hydroxide added to the guanazolo, which was made up in a concentration of 5 mg. per cc. in physiologic saline solution. It was usually injected in daily doses of 200 mg. The 7 patients who received the drug parenterally all developed a toxic dermatitis after total doses varying from 400 to 1950 mg. This toxic manifestation did not appear when...
Guanazolo was given orally. The gastro-intestinal symptoms were frequent after either oral or parenteral administration. Nausea, vomiting and diarrhea occurred. Neither intravenous nor intramuscular injections caused local pain or other reactions. The rash was of the maculopapular type. There were no changes in the blood, bone marrow or alkaline phosphatase. No subjective or objective improvement was seen, although insufficient time had elapsed to draw any definitive conclusions.

For the present study 5 patients with Hodgkin's disease were selected for evaluation of the therapeutic efficacy of guanazolo.* In order to aid in evaluation of the clinical response, only patients with acute or obviously progressive manifestations of the disease were chosen. Patients who were in an asymptomatic phase or who had had recent therapy with radiation or nitrogen mustards were excluded. A suspension of guanazolo in a virtually neutral solution was employed intramuscularly in all cases. All patients received folic acid, 10 mg. orally daily during the course of therapy.

Case 1 was a 29 year old white male with Hodgkin's disease of four years' duration. At the time of institution of therapy there was dyspnea, chest pain, weakness, cervical, axillary and mediastinal lymphadenopathy, bone involvement and anemia. The patient was resistant to roentgen and nitrogen mustard therapy. Although conscious and rational he appeared to be terminal. Treatment was instituted with 100 mg. of guanazolo daily. On the fourth day of therapy, after receiving 400 mg. of guanazolo, the patient died. Nodes in the left cervical and axillary regions appeared to have regressed in size. The drug did not appear to have influenced the unfavorable outcome. No toxic effect was noted. The injections were tolerated without pain.

Case 2 was a 18 year old white male with Hodgkin's sarcoma of two years' duration. Disease manifestations at the time of institution of therapy were weakness, dyspnea, substernal pain, fever and cervical, axillary and mediastinal lymphadenopathy. He was given guanazolo, 50 mg. daily for sixteen days, for a total of 800 mg. There was a slight increase in the size of the nodes during therapy. Toxic manifestations consisted only of pain and tenderness at the site of the injections. The patient has since responded to roentgen therapy.

Case 3 was a 53 year old white male with Hodgkin's granuloma of approximately one year's duration, manifested by fever, pruritus, generalized lymphadenopathy and anemia. Guanazolo was given in doses of 50 mg. daily for fourteen days for a total dose of 700 mg. Although the fever subsided after one week's treatment, no conclusion regarding a causal effect of the drug could be drawn. Toxic reactions were severe pain and tenderness at the site of injections in the buttocks.

Case 4 was a 35 year old white male with Hodgkin's granuloma of two years' duration. Manifestations at the time of institution of therapy were fever, axillary, pulmonary, bone and mediastinal involvement. The patient was given 50 mg. of guanazolo daily for fourteen days for a total dosage of 700 mg. Under therapy, the nodes actually increased in size. No effect on the fever was noted. Toxic reactions were limited to severe pain and tenderness at the site of injection. Radiation therapy was then instituted with improvement.

Case 5 was a 37 year old white male with Hodgkin's granuloma of five years' duration. Findings at the time of institution of therapy were fever, malaise, night sweats, generalized lymphadenopathy, jaundice, anemia and hepatosplenomegaly. He was given 50 mg. of guanazolo daily for seven days. This

* Guanazolo was supplied through the courtesy of Dr. J. M. Ruegsegger of the Lederle Laboratories Division, Pearl River, New York.
was increased to 100 mg. on the eighth day. The patient's condition was grave, and since there was no response to guanazolo, the drug was stopped and nitrogen mustard therapy was given with a dramatic response. The toxic manifestations consisted of pain and tenderness at the site of injections. Prior to institution of therapy with guanazolo, a lymph node biopsy was done and the node was grown in tissue culture. The effect of guanazolo on the tissue culture in a dose of 25 mg. per gram was determined. No inhibition of growth was observed. Thus, the in vitro response paralleled the in vivo effect.

All patients had careful studies of renal, liver and cardiac function during the course of therapy. No effect was noted. In the dosage employed, no skin manifestations were seen. Bone marrow examinations were performed before and after therapy.† There was no apparent change.

**SUMMARY**

Five patients with active Hodgkin's disease were treated for a period varying from four to eighteen days with an antiguanine preparation, guanazolo (5-amino-7-hydroxy-1H-v-triazolo[d]pyrimidine) with a total dosage of 400 mg. to 800 mg. intramuscularly. No therapeutic effect was observed. The only toxic manifestations were pain and tenderness at the site of injection in 4 of the 5 cases. The effect of guanazolo on tissue cultures of an involved node was tested. No inhibition of growth was observed, thus paralleling the lack of in vivo effect.

**REFERENCES**

2. HITCHINGS, G. H., ET AL.: Unpublished data. From Kidder, Dewey and Parks.†

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