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Phenothiazine and Androgen Treatment in Patients with Sickle-Cell-Thalassemia and Sickle-Cell Anemia

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In 1964 Lewis[1] found that phenothiazines inhibited sickling phenomenon in vitro. Later it was suggested that these compounds were successful in the treatment of clinical crises of sickle cell anemia.[2]

It is well known that androgens cause hematological improvements in different types of anemia in which the erythropoietin level is not reduced.[3] We also have studied the effects of phenothiazines and androgens on patients with sickle-cell anemia.

Methods and Materials

Hemograms were obtained using standard techniques.[4] Hemoglobin (Hb) concentration was determined by the cyanmethemoglobin method. The microhematocrit (Hct) was used for measuring packed cell volume, and the sickling test was made with 2 % sodium metabisulphite. The starch gel electrophoresis was performed according to the method of Smithies,[5] and the agar gel according to Robinson et al.[6] Fetal hemoglobin value was determined by the alkali denaturation method of Singer et al[7] and quantitative estimation of Hb A2 was obtained by chromatography on diethyl amino ethyl cellulose (DEAE)[8]

From 1966 to October 1970 Flumazin (a phenothiazine compound) was given to 28 patients with sickle - cell anemia. These patients were

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followed in the Outpatients Department of Hacettepe Children's Hospital. The doses given to the patients were fairly low, being adapted according to the patient's tolerance.

Between November, 1969 and November, 1970 a testosterone compound was given to 6 patients with sickle cell anemia and 2 with sickle cell thalassemia combinations (in the dose of 2 mg/kg.) Diagnosis was madeby performing hemoglobin electrophoresis, on starch and agar gel from the patients and their parents.

Results

With phenothiazine treatment there was no inhibition of sickling phenomenon and no beneficial effect on the frequency and severity of the clinical crises. An evaluation of the response to the treatment with flumazin was made, comparing the frequency of crises in each patient while under treatment with that preceeding the treatment. Repeated sickling tests were done during the treatment. Hb and Hct determinations were made on the patients under the testosterone treatment once a week for the first two weeks and subsequently once a month. The rises in the Hb and Hct values were compared with the patient's highest level of Hb and Hct which had been obtained on the previous visits prior to the study.

Seven out of 8 patients under testosterone treatment showed a significant rise in Hb and Hct values. (Table 1). There was no response in one.

TABLE I

THE Hb AND Hct LEVELS IN PATIENTS WITH SICKLE CELL ANEMIA, BEFORE AND AFTER ANDROGEN TREATMENT

	Hb			Hct		
Name	Bef. Ther.	Af. Ther.	Δ Hb	Bef. Ther.	Af. Ther.	Δ Hct
M.K.	7.05	8.14	1.09	21	24	3
İ.Ö.	8.15	9.05	0.9	27	29	7–2
S.O.	8.30	9.37	1.07	27	29	2
R.A.	8.30	9.05	0.75	26	27	1
N.H.	5.48	8.75	3.27	19	26	7
H.K.	7.66	9.21	1.55	22	27	5
M.K.	6.45	7.50	1.05	22	23	1
		Mean 1.39∓0.7			Mean 3∓2.2	
		P< 0.001			P< 0.01	

Testosterone did not have any influence on the frequency and severity of the crises but, as a subjective sign, the patients stated that they were feeling stronger.

Discussion

The inhibition of sickling in vitro by phenothiazines suggested the usage of these compounds in treatment of clinical crises of sickle-cell anemia. In various centers these compounds have been used in patients with sickle cell anemia without any clinical response.[9 10] This failure as emphasized by some authors[10] might be due to the insufficient quantity of phenothiazine in blood. It was shown in vitro that to produce 50% inhibition in sickling phenomenon 100-150 μg/per ml. of blood may be requried.[11] The dosage used in the treatment could not give a concentration greater than 40 μg/per ml. of blood.[11]

In 1959 Gardner noticed that patients with aplastic anemia shows increased erythropoeitic activity at the time of puberty.[12] It is well known that after puberty there is an increase in Hb and Hct levels.

Adult patients with hereditary spherocytosis and with non spherocytic anemia have higher Hb and Hct values than children with the same diseases.[13] In 1962 it was shown that exogenous androgens increased Hb and Hct values in patients with sickle-cell anemia and thalassemia.[12] In a study done in 1969, a significant rise of Hb and Hct levels of the patient with sickle-cell anemia by oxymethalon was observed.[14]

The treatment had no significant effect on the sickling tendency, of the erythrocyte and there was no alteration of the red cell survival.[15] The rise in the red cell mass, in Hb and Hct concentration was shown.[15] Our findings are in agreement with their observations.

The use of androgens for a long period, even the ones with reduced virilisation effect, in girls and in boys before puberty may show some undesirable side effects. They may be used in patients, however, after puberty to support general wellbeing and to maintain the Hb and Hct values at higher levels.

Summary

Flumazin was given to 28 patients with sickle cell anemia without significant clinical response. Out of 8 patients treated with testosterone, there was a significant rise in Hb and Hct values in seven. There was no response in one.

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