Oxymetholone Treatment for Sickle Cell Anemia

By Raymond Alexanian and Judith Nadell

Seven patients with sickle cell anemia were treated with oxymetholone for at least 2 mo. Markedly increased basal rates of hemolysis and erythropoiesis were confirmed. The urinary erythropoietin excretion was either normal or lower than expected for the red cell mass, and an expanded blood volume was due primarily to an increased plasma volume. After androgen therapy, six patients demonstrated more than a fivefold increase in urinary erythropoietin, with an increase in red cell mass ranging from 17%–75% above the control value. All showed a decline in serum iron level to the 25–75 μg/100 ml range within 4 wk after the start of therapy. Less marked changes followed lower oxymetholone doses. Reversible hepatic toxicity, with a serum bilirubin concentration exceeding 50 mg/100 ml, occurred in one patient. Androgenic hormone therapy may be useful for selected adult patients with sickle cell disease when severe anemia contributes to disease morbidity.

DISEASE MORBIDITY in most patients with sickle cell anemia usually results from painful "crises," or from the end results of multiple organ infarctions. In addition, some patients are symptomatic from severe anemia due to markedly increased rates of red cell destruction. Androgenic hormones are useful in some patients with anemia due to bone marrow failure,[1,2] and recent studies have defined erythrokinetic criteria from which to predict clinical benefit in individual patients.[3,4] Androgens have been reported useful in some patients with sickle cell anemia,[5,6] but recent reviews on treatment have devoted little attention to this mode of therapy.[7] No studies in patients with sickle cell disease have been conducted with oxymetholone, an oral androgen of the 17-alpha alkylated class. This report summarizes an evaluation of erythrokinetics and of oxymetholone treatment trials in seven patients with sickle cell anemia. Results indicate marked elevations in erythropoietin excretion and in red cell mass in most patients, even though basal rates of erythropoiesis were already markedly increased.

MATERIALS AND METHODS

Patient Characteristics

Seven patients with sickle cell anemia had erythrokinetic studies before and during treatment with oxymetholone. Their ages ranged from 14 to 48; five were male; all were black. Pain crises were infrequent in all, averaging less than two per year during the preceding 3 yr. All were symptomatic from anemia by virtue of easy fatigability and/or dyspnea on exertion. Anemia was severe in all, with the hematocrit ranging from 20–26 vol/100 ml (Table 1). The serum iron exceeded 65 μg/100 ml, and the fetal hemoglobin concentration was less than 10% in all. The

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Table 1. Erythrokinetic Features in Patients With Sickle Cell Anemia

Patient	Age	Hct (Vol/100 ml)	Reticulocyte Index[8]	Serum Fe (μg/100 ml)	$^{59}T\frac{1}{2}$ Plasma Fe Clearance (min)	Erythron Iron Turnover (mg/100 ml blood/day)	$T\frac{1}{2}^{51}Cr$ Labeled Red Cells (days)	Plasma Volume (ml/sq m)	Red Cell Mass (ml/sq m)	Total Blood Volume (ml/sq m)
M.J.	43	26	7.4	73	27	1.78	8	2220	560	2780
M.O.	15	23	8.3	130	25	3.65	12	2550	530	3080
H.R.	15	22	6.3	100	24	2.98	9	2480	590	3070
R.T.	48	25	11.0	250	47	3.33	11	2590	600	3190
S.Y.	14	20	7.2	88	24	2.68	8	1920	390	2310
K.Y.	17	20	7.3	66	19	2.44	8	2540	510	3050
A.C.	14	23	8.1	98	24	2.88	8	2440	580	3020
Normal range		42–50	0.7–1.5	86–137	69–129	0.35–0.55	26–34	1170–1540	900–1250	2060–2670

reticulocyte concentration exceeded 12%, and the reticulocyte index corrected for the hematocrit ranged from 6.3 to 11.0.[8] The creatinine clearance was greater than 30 ml/min in all patients. All patients were maintained on oral folic acid 1 mg/day for at least 4 wk prior to any studies.

Erythrokinetic Studies

The rate of red cell production was defined from the erythron iron turnover. Plasma iron turnover studies were conducted with ^{59}Fe and the erythron iron turnover was calculated as described previously.[4,9] In all patients, the rate of red cell production exceeded 4 × normal, and linear body scanning showed evidence of bone marrow expansion in the extremities.[10] The red cell mass and red cell survival were measured with ^{51}Cr.[11] The red cell mass ranged from about 40%-60% of normal and the half-time for disappearance of ^{51}Cr labelled red cells was 12 days or less in all (Table 1). The plasma volume was measured simultaneously with ^{125}I-labeled albumin, (Albumotope, E. R. Squibb & Sons, Inc.) and the total blood volume derived from the sum of the measured red cell and plasma volumes. The urinary erythropoietin excretion was measured as described previously, with results expressed as Standard B units/day.[12,13]

Androgen Treatment

Oxymetholone was administered to all patients in an initial daily dose of 40 mg/sq m to the 2 females and of 160 mg/sq m to the five males.* In the absence of side affects, the dose was increased by 50% at monthly intervals for a minimum 9-wk treatment period. The mean daily dose to the women was 63 mg/day, and to the men 268 mg/day. Hematocrit, liver function studies, and serum iron concentration were monitored at monthly intervals. The red cell mass was remeasured with ^{51}Cr after at least 2 mo of androgen therapy.

RESULTS

The red cell mass increased from 17%–75% above the control level in six of the seven treated patients in association with a hematocrit increment of at least 5 vol/100 ml. The only exception was patient A.C., who developed hepatic toxicity after 2 mo, with no change in red cell mass or hematocrit. The median elevation in red cell mass for all was 190 ml/sq m, which represents about one-third of the red cell mass in these patients and about 20% of the mass in normal man (normal range 900–1250 ml/M^2). The plasma volume remained unchanged in all five patients with measurements before and after at least 2 mo of therapy (Fig. 1). The ratio of the body hematocrit to the venous hematocrit ranged from 0.75 to 0.85, and also did not change. Serum iron concentration declined markedly to levels ranging from 25 to 75 μg/100 ml after one mo of treatment, with a decline of at least 25 μg/100 ml within 4 wk in all patients (Fig. 1). Serum iron values recovered to the control range within 2 wk after oxymetholone was terminated.

No change in red cell survival was noted during the period of oxymetholone treatment in two patients with detailed studies. Figure 2 demonstrates the similar slope for the disappearance of ^{51}Cr-tagged red cells in one patient (R.T.) during and immediately following the termination of oxymetholone treatment. In this study, ^{51}Cr-tagged red cells were injected 10 days before completion of the oxymetholone trial when the hematocrit had increased from 25% to 31%; the survival studies were continued until 14 days after termination of oxymetholone, when the hematocrit had declined to 24%. As indicated in Fig. 2, no evidence of a shortened red cell survival was found during the control period following the cessation of therapy.

*Written informed consent was obtained from all patients.

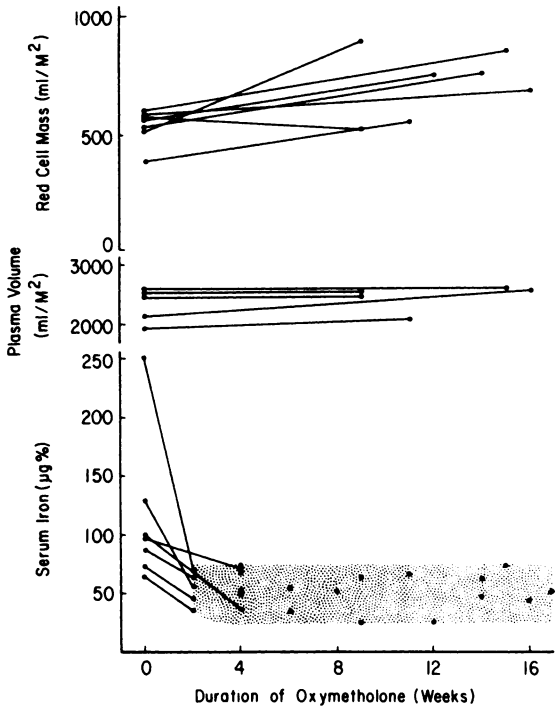


Fig. 1. Changes in red cell mass, plasma volume and serum iron concentration during oxymetholone treatment. Substantial elevations in red cell mass were associated with no change in plasma volume and with serum iron values declining within 4 wk to the 25–75 µg/100 ml range. The shaded area includes the range for all serum iron values after the first 2 wk of treatment.

Urinary erythropoietin excretion was measured before and during androgen treatment. Figure 3 compares pretreatment values with results after 1 mo of therapy. Basal erythropoietin excretion was either normal or lower than predicted for the red cell mass, but the posttreatment excretion increased by more than 5 x the value predicted for the new red cell mass in all but one patient. Since the red cell mass was not measured after 1 mo of treatment, values after 4 wk of androgen were derived for each patient from the curves in Fig. 1 at the time of the urinary erythropoietin collection. Both women showed a marked enhancement of erythropoietin excretion after 1 mo, despite their lower daily dose of oxymetholone (Fig. 3).

After an interval of at least 4 wk, four patients were retreated with mean daily oxymetholone doses ranging from 25%–40% of their initial dose. The decline in serum iron concentration was less marked (i.e., to the 55–90 µg/100 ml range), the increase in urinary erythropoietin was less (i.e., two of three

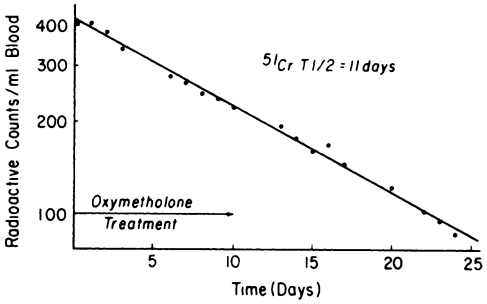


Fig. 2. The rate of disappearance of ^{51}Cr-labeled red cells in a patient with sickle cell anemia during the final 10 days of an oxymetholone treatment trial when the hematocrit was 31%, and for 14 days after oxymetholone was terminated when the hematocrit fell to 24%.

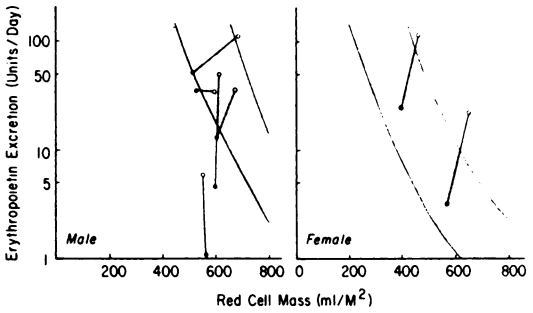


Fig. 3. Effect of oxymetholone treatment on urinary erythropoietin excretion in patients with sickle cell anemia. Solid circles indicate basal values and open circles the urinary erythropoietin after 1 mo of oxymetholone therapy. The shaded area indicates the range for the relation between erythropoietin and red cell mass in 90% of 36 patients with varying degrees of anemia due to bone marrow failure.

with evaluable studies did not achieve a fivefold stimulation), and there was less elevation in red cell mass (i.e., reaching less than 650 ml/sq m in all), in comparison with the superior results after their initial treatment trial.

Most patients tolerated oxymetholone with a low frequency and degree of side affects. Two male patients receiving high doses had muscle aching, one woman demonstrated increased virilization, and one male developed hepatic toxicity. In this patient (A.C.) with marked jaundice, the total bilirubin increased from 5.5 mg/100 ml to 52 mg/100 ml after 2 mo of treatment with only a slight elevation in liver enzyme values and no change in serum alkaline phosphatase. Within 6 wk after the termination of oxymetholone, the bilirubin level had returned to the pretreatment range. No side affects occurred in any of the patients receiving the low oxymetholone doses. No apparent change occurred in the frequency of "pain crises."

The blood volume was evaluated in all seven patients treated with oxymetholone, as well as three additional untreated patients. Basal values for total blood volume were above the upper limit of the normal range in all but one (Fig. 4); the plasma volume was also higher than predicted for the hematocrit in the same patients with an increased blood volume. The expanded plasma volume accounted completely for the measured increase in blood volume. The mea-

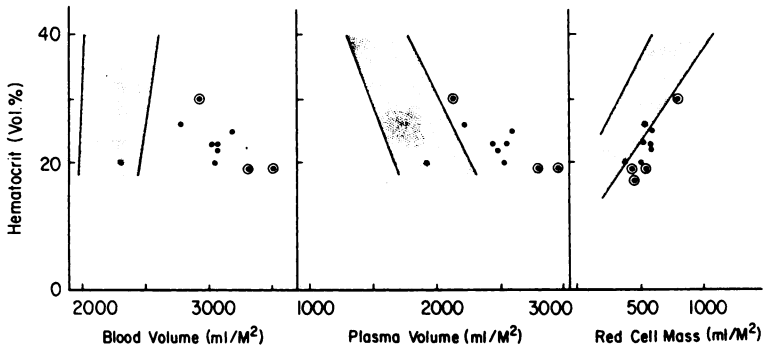


Fig. 4. Basal values for blood volume, plasma volume and red cell mass in patients with sickle cell anemia. The solid circles indicate measurements in comparison with the ranges for 46 measurements in 34 patients with anemia due to marrow failure. No patients with splenomegaly or serum monoclonal gammopathy were included in the control ranges. The circled values represent patients with blood volume studies who did not receive androgen treatment; in one of these patients, only the red cell mass was measured.

sured red cell mass was greater than predicted for the hematocrit in most patients (Fig. 4). There was no significant correlation between the magnitude of the expansion of total blood volume and the degree to which erythropoietin excretion was depressed below the level predicted for the red cell mass.

DISCUSSION

This study evaluated the clinical utility of oxymetholone, an oral androgen of the 17-alpha alkylated class, in patients with sickle cell anemia. All showed evidence of severe hemolysis and markedly increased basal levels of red cell production. All patients had an adequate iron supply, adequate renal function, and were provided with supplemental folic acid. The urinary erythropoietin excretion was assessed serially as an index of changes in erythropoietin production. No overt complicating factors were present, such as infection, that might have impaired maximal levels of bone marrow activity.

All patients demonstrated basal levels of erythropoietin that were either appropriate or depressed for the degree of anemia. Erythropoietin values less than predicted for the red cell mass in some patients with sickle cell anemia may be due to the increased blood flow, and the anatomic expansion of the bone marrow, that may have compensated more effectively for the increased tissue requirements for oxygen in comparison with other anemic states.[14,15] In addition, the red cells in sickle cell anemia are considered to have a low oxygen affinity with a shift of the oxygen dissociation curve to the right.[16,17] The improved oxygen delivery from this adjustment may further inhibit the need for a maximal increase in erythropoietin and red cell production.[18] Finally, this report confirms a markedly increased total blood volume in most adults with sickle cell anemia. The total blood volume was about 50% greater than that found in other patients with anemia due to bone marrow failure and was due primarily to marked elevations in plasma volume. The mechanism for the increased plasma volume was not determined, but this change was associated with a decreased body hematocrit/venous hematocrit ratio. Thus, in contrast to the conclusions reached for children,[19] most adults with sickle cell anemia have an expansion of total blood volume that may contribute substantially to an increased oxygen transport. Erlandson also reported an increased plasma volume in children with sickle cell anemia in comparison with children anemic from other hemolytic anemias.[20]

All patients but one demonstrated significant elevations in red cell mass following at least 2 mo of oxymetholone treatment. The frequency and magnitude of this stimulation were similar to the experiences of others using parenteral testosterone.[5,6] The increased red cell mass in all studies was usually of moderate degree, and was attributed to a further stimulation of red cell production. This conclusion was supported by our failure to detect any changes in red cell survival in two patients and the marked decline in serum iron concentration during the oxymetholone treatment period. Lundh also failed to detect any reproducible alteration in red cell survival in three patients.[5] The median rate of red cell production in our patients was about six times normal, a level similar to that reported by others.[9,20] Finch has demonstrated that the human bone marrow is capable of producing red cells at more than this level, provided ade-

quate iron supplies are maintained.[9] These findings confirm that further bone marrow stimulation will occur in most patients with sickle cell anemia despite their high basal rate of erythropoiesis. Less stimulation of erythropoiesis was found with lower oxymetholone doses, suggesting a dose-response relationship between androgen dose and the magnitude of the increase in red cell production.

Consistent reductions in serum iron concentration were noted in all patients within several wk after the start of androgen treatment. This decline was similar to that found in some patients with bone marrow failure,[4] in women with breast cancer,[21] and in elderly men with osteoporosis,[22] who developed an increased red cell production during androgen treatment. In the absence of any documented changes in the hemolytic rate, such reductions in serum iron level were attributed to an increased magnitude of iron turnover to the bone marrow in subjects with stimulated erythropoiesis. A less likely possibility is that androgens may effect iron metabolism in a manner unrelated to erythropoiesis.

No changes in plasma volume were detected in five patients after at least 2 mo of oxymetholone therapy. Boada and Frumin reported an unchanging or increased plasma volume in four patients with sickle cell anemia treated with nandrolone.[6] Lundh and Gardner calculated a decrease in plasma volume in patients with sickle cell anemia who also received nandrolone.[5] Several explanations may account for the varying conclusions concerning plasma volume. Lundh and Gardner estimated plasma volume in their patients from the venous hematocrit and the red cell mass in contrast to the direct measurements in our study. Secondly, the treatment period was 8 wk or less in all but 2 of the 11 patients treated by Lundh, while all of our patients received at least 9 wk of treatment; thus, transient declines in plasma volume during the early treatment period may have been missed in our study. Finally, major differences were present in the nature and schedule of the different androgens used in these studies. Of interest is that Gardner had previously reported elevations in plasma volume of more than 25% in 4 of 15 elderly males with osteoporosis treated with nandrolone, emphasizing the difficulty in interpreting slight changes in hematocrit during the early treatment period.[22]

The urinary erythropoietin excretion increased at least fivefold in all but one of our patients. Similar elevations have been documented in patients with bone marrow failure who received identical oxymetholone doses.[4] This finding suggests that the increased erythropoiesis induced in androgen-treated patients with sickle cell anemia resulted from a stimulation of erythropoietin production. Gordon has demonstrated that androgens enhance erythropoiesis in animals by increasing the production of a renal erythropoietic factor (REF).[23] Whether oxymetholone also stimulated the bone marrow of these patients by other mechanisms independent of erythropoietin was not evaluated in this study. Levere has provided evidence for a direct action of certain androgens on erythroblasts.[24] Androgens may result in more cells sensitive to erythropoietin by triggering more plutipotential cells from a G_0 phase to a G_1 phase responsive to erythropoietin.[25] Gorshein and Gardner concluded that 19-nortestosterone decanoate stimulates a larger number of erythropoietin-sensitive cells that may protect the bone marrow from the affects of Actinomycin D.[26] Thus, increasing

evidence supports a dual role for androgens on erythropoiesis, the first from a stimulation of erythropoietin production and the second from an increased proliferation of primordial cells sensitive to erythropoietin.

All but one of the patients tolerated their androgen treatment without major side affects. In the one patient who developed hepatic toxicity, the marked hemolytic anemia undoubtedly contributed to the magnitude of the hyperbilirubinemia (i.e., to more than 50 mg/100 ml). Although a larger number of red blood cells susceptible to sickling was produced in most patients, there was no increase in the frequency of pain crises. In contrast to the high frequency of priapism following large doses of parenteral testosterone,[5] this complication did not occur in any of our adult males receiving oxymetholone. However, our patients were probably less likely to develop crisis or priapism since such episodes were rare prior to their androgen treatment.

These findings demonstrate the potential value of androgens in the treatment of selected patients with sickle cell disease when severe anemia contributes substantially to disease morbidity. Only patients with a low frequency of crises should be considered in order to avoid the increased incidence that might result from a greater production of sickle hemoglobin. Few children are likely to be suitable candidates, since most of their problems usually result from repeated painful crises rather than from severe anemia. However, adults with evidence of major organ damage may be less able to compensate adequately for anemia. This applies particularly to patients with evidence of cardiac or pulmonary disease who may benefit from the higher red cell mass that usually results from androgens. The potential value in individual patients must outweigh the real risk of hepatic toxicity that will develop in about 10% of the patients.[4] Consequently, the initial treatment trial should not continue for more than 3 mo. If no substantial benefit results in terms of symptomatology and hematocrit, or if liver toxicity occurs, the androgen used should be discontinued permanently. Even when significant improvement occurs, androgen therapy should still be terminated after 3 mo. The magnitude of relapse in terms of both subjective and objective manifestations will then allow the clinician a better opportunity to define the potential value of long-term androgen therapy for his patient.

Recently, cyanates have been found to increase the hemoglobin level and decrease the hemolytic rate as the result of carbamylation of the amino-terminal valine of hemoglobin.[27] However, doses of sodium cyanate greater than 35 mg/kg produced clinical side-effects.[27] Combinations of androgens and cyanates in doses free of toxicity for both agents may provide superior results than either compound alone.

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