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Oxymetholone in aplastic anaemia

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Summary

Thirty-one patients with aplastic anaemia were treated with oxymetholone. Twenty-eight patients lived beyond 2 months and of these eleven patients showed clinical and haematological improvement. Ten of these had some active erythropoietic areas as shown by bone marrow biopsies and by the presence of an elevated reticulocyte count in the peripheral blood. Two patients who responded in spite of a markedly hypoplastic marrow and reticulocytopenia became oxymetholone dependent and relapsed when the drug was withdrawn. They failed to respond a second time when oxymetholone was re-introduced. Side effects were frequent. These were mostly tolerable and reversible on reduction of the dose but three patients died of acute myeloblastic leukaemia and in three others the drug had to be withdrawn.

DURING recent years androgenic hormones have been used extensively in aplastic anaemia (Shahidi and Diamond, 1961; Sanchez-Medal *et al.*, 1964; Reynafarje and Faura, 1967; Daiber *et al.*, 1970). Promising reports have appeared in favour of oxymetholone which is an oral androgen. Sanchez-Medal *et al.* (1969) claimed a remission rate of 70% in patients with aplastic anaemia who lived longer than 2 months and thus received an adequate trial with oxymetholone. Similar results have been reported by Allen *et al.* (1968) and by Silink and Firkin (1968).

We present here our experience with oxymetholone on thirty-one patients with aplastic anaemia.

Patients and methods

Thirty-one patients were treated. All had pancytopenia and a marrow with reduced cellularity at some stage on serial trephine biopsies. In nine patients aplastic anaemia was considered to be drug-induced (Table 1). All other causes of anaemia were excluded by a careful clinical assessment and by haematological investigations. Patients with primary disease affecting the bone marrow by infiltration or by replacement of active haemopoietic tissue were excluded.

Haematological investigation and ferrokinetic studies were performed by standard methods (Dacie and Lewis, 1968). All patients had a sternal marrow aspiration and a trephine biopsy on the iliac crest. Both these procedures were repeated on seventeen patients to define the extent of aplasia and to assess the response to therapy. Sixteen patients died and autopsies were performed on nine. In these patients sections from the pelvis and from the vertebral column were examined histologically to get an overall picture of the marrow cellularity. Marrow cellularity was divided into the following sub-headings according to the observations made on the trephine sections:

(a) Marked hypoplasia. The trephine sections showed an occasional collection of lymphocytes or reticulum cells among the fatty cells. There was a severe depression of the erythro-myeloid elements and a complete absence of megakaryocytes.

(b) Moderate hypoplasia. A marked reduction of the overall cellularity but an occasional island of

normal erythroid or myeloid series was seen. No megakaryocytes were found.

(c) Mild hypoplasia. A general reduction in the cellularity but scattered among areas of complete aplasia were some foci of normal marrow elements. There were no megakaryocytes.

(d) Patchy hypoplasia with hyperplasia. Two patients (cases 9 and 27) were found to have foci of increased cellularity with some patches devoid of cells. Megakaryocytes were severely reduced or absent.

Oxymetholone was administered orally in a dosage of 3–5 mg/kg a day to all the thirty-one patients. This dose was reduced to 1.5–2 mg/kg/day in the surviving patients after 2 months. More than half the patients were receiving prednisolone before the therapy with oxymetholone. Corticosteroids were gradually tailed off although some patients were maintained on 10 mg of prednisolone a day.

Results

Of the thirty-one patients treated with oxymetholone, three died within the first 4 weeks. Since treatment with oxymetholone takes about 2 months to produce a worthwhile therapeutic effect (Allen *et al.*, 1968; Sanchez-Medal *et al.*, 1969), these three patients were excluded from the final consideration.

Table 1 shows the initial clinical and haematological data of the remaining twenty-eight patients. There were thirteen males and fifteen female patients. The average age of the whole group was 45 years. The shortest duration of symptoms before the first presentation was one week (case 19) and the longest 2 years and 8 months (case 2). The average duration of symptoms before the first medical attendance was 6.6 months. The presentation of symptoms tended to be more acute in patients where a toxic agent could be incriminated. The idiopathic cases on the other hand had a more insidious onset.

Response to oxymetholone

Complete remission was considered to have occurred if all the peripheral blood indices returned to normal and if the marrow showed evidence of regeneration on subsequent examinations. There was only one instance of complete remission (case 19) when the peripheral blood picture returned to normal in 7 months from the onset of treatment with oxymetholone. The bone marrow which was markedly hypoplastic before treatment showed erythromyeloid areas of regeneration on subsequent examination. However, the aplastic state reappeared

TABLE 1. Clinical and haematological details of twenty-eight patients on first admission

No.	Name	Age (years)	Sex	Duration of symptoms*	Hb (g%)	WCC $10^3/\text{mm}^3$	Platelets $10^9/\text{mm}^3$	Reticulocytes %	Marrow
1	RF	28	M	2	8.1	2.5	25	n.d.	a
2	JB	21	F	32	7	3	32	0.5	a
3	CS	75	F	12	4.7	2.7	33	3.6	b
4	HB	16	F	16	3.2	2.5	14	2.2	c
5	RH	42	M	6	4.7	2	10	n.d.	a
6	WG	52	M	2	6.5	2.6	50	0.8	b
7†	PB	18	F	1	13	3.2	9.4	0.5	b
8†	EM	72	F	2	5.8	2	22	2.8	b
9†	JG	52	M	1	8	3.4	27	none	d
10	RM	30	M	2	5	2.8	10	0.8	b
11	DC	18	M	1	6.5	4.6	9	0.5	b
12†	HK	68	F	12	9.5	8.8	76	8	c
13†	ND	59	F	12	7.9	2.2	8	0.5	a
14	NJ	39	F	incidental	7.2	1.4	148	2.3	c
15†	LK	58	F	2	9	2	7	0.8	a
16	CF	26	F	0.5	6.2	2	9	0.2	a
17	AS	69	F	5	8.6	3	79	n.d.	a
18	GG	48	M	3	10	3.7	49	0.8	b
19	AM	38	M	0.25	6.2	3	6	none	a
20†	WH	68	M	incidental	7.1	2.2	11	0.2	b
21	JC	67	F	1	6.9	3.8	8	n.d.	b
22†	LS	55	F	9	10.9	4.6	7	0.5	b
23	DF	4	M	1	3	8.4	8	3	b
24	RD	57	M	24	7	4	70	4.9	b
25	BS	39	F	6	6.1	3.9	10	1.8	b
26†	WT	60	M	1	8	3.1	31	3.7	b
27	DH	48	F	24	5.4	3	6	n.d.	d
28	AE	18	M	unknown	10.2	2.8	11	n.d.	b

a = marked hypoplasia; b = moderate hypoplasia; c = mild hypoplasia; d = patchy hypoplasia with hyperplasia; n.d. = not done.

* Duration of symptoms in months before first medical attendance.

† Secondary to a toxic agent.

when the therapy was discontinued as shown in Fig. 1. Treatment with oxymetholone was restarted and the patient was also put on prednisolone but he failed to improve and died from septicaemia and generalized haemorrhage. Ten other patients showed a partial response with an appreciable improvement in

FIG. 1. Haematological response to oxymetholone in a patient (case 19) with aplastic anaemia. The marrow aplasia relapsed fatally 2 months after cessation of the oxymetholone therapy. $\circ$ = Hb(g/100 ml); $\times$ = platelets ($\times 10^3/\text{mm}^3$); $\bullet$ = WCC ($\times 10^3/\text{mm}^3$).

the haemoglobin (Hb) and some increase in the white cell count (WCC). Platelets increased very slowly and counts above $100,000/\text{mm}^3$ were obtained only in three instances (Table 2). The trephine sections showed some improvement in seven patients followed over 3 years (Table 2). Case 27, however, showed a change to a marked hypoplasia on repeated trephine biopsies in spite of a clinical and haematological improvement. A favourable response was signalled by stabilization of the Hb level around 8–9 g% and an increase in the reticulocyte percentage (Table 2, Fig. 1). There was a slow increase in the WCC and a further improvement in the Hb concentration during the 6–12 weeks from the onset of therapy. Another favourable feature which foreshadowed remission in some cases was a relative increase in polymorphs. The absolute neutrophil count increased very slowly and in five cases remained between 2000 and $3000/\text{mm}^3$. A gradual proliferation of the haemopoietic tissue occurred in seven patients followed over 3 years.

Island of active erythropoiesis on the trephine sections and some reticulocytes in the peripheral blood usually heralded a good prognosis. Of the eleven patients who responded, six had a reticulocyte count of more than 2% (Table 2) and ten patients had some erythropoietic areas on the trephine sections. Out of the whole group of twenty-eight patients treated for more than 2 months, only two patients (cases 14 and 26) showed no response

TABLE 2. Pre- and post-treatment haematological data of patients responding to oxymetholone

Case No.	WCC ($\times 10^3/\text{mm}^3$)	Platelets ($\times 10^3/\text{mm}^3$)	Hb (g%)	Reticulocytes (%)	Marrow	Remarks
3	before 2.7 after 5.1	33 72	4.7 11.9	3.6 60.0	b* c*	Alive—3 years
4	before 2.5 after 4.2	14 25	3.2 12.2	2.2 7.0	c c	Needs occasional blood transfusion
6	before 2.6 after 9.2	50 40	6.5 13.6	0.8 3.0	b c	Alive—4 years
8	before 2.0 after 7.7	22 124	5.8 15.6	2.8 5.0	b c	Alive—3 years
9	before 3.4 after 5.0	27 96	8.0 12.7	none 4.2	d* d	Alive—5 months
10	before 2.8 after 3.5	10 88	5.0 13.1	0.8 3.6	b c	Alive—4 years
12	before 8.8 after 132.0	76 32	9.5 5.8	8.0 4.0	c d	Developed leukaemia
19	before 3.0 after 6.1	6 148	6.2 13.3	none 14.0	a* d	See Fig. 1
23	before 8.4 after 5.0	8 30	3.0 12.6	3.0 6.0	b c	Alive—3 years
24	before 4.0 after 4.9	70 130	7.0 10.0	4.9 5.0	b c	Lost to follow up after 18 months
27	before 3.0 after 5.9	6 76	5.4 14.7	n.d. 2.1	d a	Alive—3 years

* See Table 1.

in spite of an initial reticulocyte count of more than 2%, but both these patients are still alive with the aid of monthly blood transfusions. One patient with marked hypoplasia (case 17) responded slightly to oxymetholone but her therapy was discontinued because of the side effects (diarrhoea, acne, deepening of the voice, etc.). This withdrawal of oxymetholone was followed by a severe pancytopenia which proved refractory to a second course of oxymetholone and she died of septicaemia. These two patients (cases 17 and 19) showed oxymetholone dependence and relapsed fatally on withdrawal of the drug. It is interesting to note that these were the only two patients who responded to oxymetholone in spite of a markedly hypoplastic marrow and a peripheral reticulocytopenia.

Mortality

Sixteen patients died over the period of 4 years; three during the first month, two in the next 6 months, eight in the subsequent 16 months, and two during the next 2 years. The death rate decreased as the duration of therapy increased. The overall remission rate in the twenty-eight patients treated for more than 2 months was 39.2%.

Factors influencing mortality

A low Hb concentration did not appear to increase the risk of death (Table 3). This finding was not surprising as the patients with a low Hb. level were well supported with frequent blood transfusions. A neutropenia of less than 500/mm³ was very unfavourable as eight patients out of twelve with such meagre counts died. This mortality rate was significantly higher ($P < 0.05$) than in the neutropenic group with an absolute neutrophil count between 500 and 2000/mm³. Thrombocytopenia of less than 10,000/mm³ also carried a bad prognosis as five out of the ten patients died. The initial higher Hb level

did not influence the subsequent downhill course in patients who had a markedly hypoplastic marrow. Whatever the other haematological values, patients with marked hypoplasia of the marrow as defined here had a very grave outcome with a death rate of 88.8% (Table 3). On the other hand patients with a moderate hypoplasia had a very low mortality rate of 18.1%. The difference between the death rates in these two groups was statistically significant ($P < 0.005$).

Side effects of oxymetholone

High doses of oxymetholone given initially were well tolerated by most patients. Acne, deepening of the voice and a significant increase in the facial hair were the main complaints in four female patients (cases 2, 15, 17, and 25). One patient (case 17) also developed intractable nocturnal diarrhoea necessitating withdrawal of oxymetholone. Acne proved to be very disfiguring in case 25. Sickness and diarrhoea were experienced by one more patient (case 22) but these symptoms subsided on reduction of the dosage to 150 mg a day. Significant retention of fluid occurred in three patients (cases 17, 21 and 22) but all of these had pre-existing heart disease. Mild fluid retention developed in eight patients with an increase in weight. Six of these patients also complained of troublesome night cramps. Four patients developed mild jaundice with an impairment of the hepatic function tests (cases 7, 14, 20 and 21). In one of these (case 7) the jaundice became deeper with a serum glutamic-oxaloacetic (SGOT) level of 700 units/ml and serum glutamic-pyruvic transaminase (SGPT) level of 1500 units/ml (normal less than 30 units/ml). Abnormal values returned to normal in the surviving patients (cases 7 and 14) following cessation of oxymetholone therapy. Case 21 has not been under observation long enough to draw any conclusions. Three patients (cases 11, 12 and 20) developed

TABLE 3. Prognostic significance of haematological data

	No. of patients	Deaths	Significance (P)
Haemoglobin (g%)			
Less than 5	4	1 (25%)	
Between 5 and 8	15	6 (40%)	n.s.
Between 8 and 11.7	8	5 (62.5%)	n.s.
Neutrophils/mm ³			
Less than 500	12	8 (66.6%)	
Between 500 and 2000	8	1 (12.5%)	<0.05
Platelets/cu.mm			
Less than 10,000	10	5 (50%)	
Between 10,000 and 50,000	13	4 (30.7%)	n.s.
Marrow			
Marked hypoplasia	9	8 (88.8%)	
Moderate hypoplasia	14	2 (14.2%)	<0.005

n.s.=not significant.

leukaemia whilst on oxymetholone. This rapid transformation from hypocellular marrow to sheets of blast cells may be related to a myelostimulatory effect of oxymetholone. The case records of these patients have been reported elsewhere (Delamore and Geary, 1971).

Discussion

Oxymetholone produced an effective remission in eleven of the twenty-eight patients with aplastic anaemia treated for periods longer than 2 months. Some workers have claimed remission in a higher proportion of cases (Sanchez-Medal *et al.*, 1969; Allen *et al.*, 1968; Silink and Firkin, 1968). It is difficult to compare one series with the other in a disease where fundamental differences occur in the diagnostic criteria and in the standards set for remission by various workers. There is no entirely satisfactory definition of aplastic anaemia (Wintrobe, 1967; Mohler and Leavell, 1958). These difficulties are compounded by a tendency of this disease to spontaneous remissions and relapses (Scott, Cartwright and Wintrobe, 1959; Bomford and Rhoads, 1941) which makes evaluation of any therapy very difficult. However, the eleven patients here showed increasing reticulocytosis with an increase in the Hb concentration while on oxymetholone. A previous review of our patients before the advent of oxymetholone showed only a 25% remission rate (Israel and Wilkinson, 1961), and it would appear that oxymetholone has significantly improved the survival rate.

Androgenic steroids have long been considered to possess some stimulatory effect on the bone marrow (Pfeiffer and Gardner, 1938; McCullagh and Jones, 1942; Kennedy and Gilbertson, 1956) but the precise mechanism of this stimulation is uncertain. Patients with aplastic anaemia have a prolonged plasma iron clearance and a low red-cell iron utilization (Silink and Firkin, 1968; McCredie, 1969). These workers found that the low values return to normal following treatment with oxymetholone. Ferrokinetic studies performed on three of our patients confirmed the presence of a sub-normal plasma iron clearance and a low red-cell utilization. However, a normal plasma iron turnover in one patient on oxymetholone therapy (case 7) was unaccompanied by clinical or haematological recovery. There was an excessive deposition of iron in the marrow reticulum cells and erythroblasts without any effective erythropoiesis.

Alexanian, Nadell and Alfrey (1972) showed a five-fold increase in the urinary erythropoietin excretion following the administration of oxymetholone but haematological improvement occurred only in cases who had effective erythropoietic areas demonstrated by the marrow cellularity and by

pelvic uptake of the ^{59}Fe . In this study, ten out of the eleven patients who responded had some active erythropoietic areas on serial marrow biopsies and six of these had a peripheral reticulocyte count of more than 2% (Table 2). The reticulocyte count increased with the clinical improvement and the marrow showed a gradual cellular proliferation. This regeneration proceeded unexpectedly to the formation of sheets of blast cells in three patients who died with leukaemia. The major site of action of androgenic steroids appears to be in the bone marrow. The results of other workers support this conclusion (Reynafarje and Faura, 1967; Jepson and Lowenstein, 1967).

In one patient (case 27) the initial increased cellularity regressed and the subsequent trephine sections showed a marked hypoplasia in spite of an adequate clinical and haematological response. The pretreatment hypercellularity probably represented clones of ineffective erythropoietic areas which regressed with treatment and a gradual proliferation of the normal areas elsewhere ensued to produce the haematological remission. It is also possible that misleading biopsies were obtained although the trephine sections were taken from both iliac crests.

The presence of cellular foci did not appear to influence the prognosis in patients studied by Lewis (1965). Vincent and de Gruchy (1967) found no correlation between the initial haematological values and ultimate survival. Other workers (Bomford and Rhoads, 1941; Mohler and Leavell, 1958) showed a better prognosis associated with the presence of cellular foci in the marrow. Alexanian *et al.* (1972) concluded that patients with markedly depressed erythropoiesis derived no benefit from oxymetholone. In this study, patients with cellular areas on the trephine sections had a better prognosis and appeared more likely to respond to oxymetholone. Marked hypoplasia of the marrow and severe neutropenia ($<500/\text{mm}^3$) carried a significantly adverse prognosis (Table 3). Four patients who died within the first 3 months showed a progressive fall in their absolute neutrophil count. The patients who responded to oxymetholone, on the other hand, showed a gradual increase in neutrophils. The platelet count remained low and did not provide any prognostic indication although patients with less than $10,000/\text{mm}^3$ fared badly.

Some workers recommend withdrawal of oxymetholone when a patient has remained in remission for a few weeks. Relapses following such withdrawals have not been uncommon (Allen *et al.*, 1968; Sanchez-Medal *et al.*, 1969). However, seven out of the eight patients who relapsed responded to oxymetholone for the second time in the group studied by Sanchez-Medal and his co-workers (1969). Two of our patients failed to respond to oxymetholone

when re-introduced following a short withdrawal. Unlike the other patients who remitted on oxymetholone, these two patients had responded despite a markedly hypoplastic marrow. It would seem that if the patients with severe aplasia respond they may become wholly oxymetholone dependent and should be kept on the drug till there is a definite evidence of repopulation of the bone marrow. The withdrawal of therapy in such cases should be very slow and cautious.

In conclusion oxymetholone appears to be of definite value in patients with some erythropoietic areas in the marrow but the prognosis in patients with marked hypoplasia remains very grave.

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The use of dicobalt edetate (Kelocyanor) in cyanide poisoning

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Summary

A case of accidental poisoning with sodium cyanide is reported. The patient was treated with a new antidote, dicobalt edetate (Kelocyanor). Blood levels of cyanide were shown to fall markedly.

Introduction

The standard treatment of cyanide poisoning has been the rapid intravenous administration of sodium nitrite followed by sodium thiosulphate (Chen, Rose and Clowse, 1934; Chen and Rose, 1952, 1956).