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METHANDIENONE IN LONG-TERM CORTICOSTEROID THERAPY¹

By

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Earlier experience with anabolic agents has proved disappointing. Most anabolic agents available for therapeutic use at present are testosterone derivatives and those which possess an appreciable role in proteogenesis appear to have virilizing side-effects. Norethandrolone employed in doses sufficient to produce nitrogen retention and stimulate muscle growth and increase in weight produces virilizing effects in women and in children. Although 19-nor-Androstenolone is less liable to produce such side effects, the use of this steroid is limited in practice by virtue of the fact it can be administered only by parenteral injection.

Methandienone ("Dianabol") is 1-dehydro-17- α -methyltestosterone, with a structural formula similar to methyltestosterone but possessing an additional double-bonding in the first benzene ring between carbons 1 and 2.

Experimental work on rats had already shown that Methandienone had an anabolic action comparable with or even greater than that of other anabolic steroids, it had an androgenic effect approximately only one hundredth that of testosterone propionate (*Desaulles et al.* 1959). Moreover it was active when given by mouth. From an earlier clinical trial of Methandienone in selected cases of chronic or recurrent infection associated with progressive loss of weight or with failure to regain lost weight, encouraging results had been obtained. Three out

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Methandienone
(1-Dehydro-17
+Methyltestosterone-
"Dianabol")

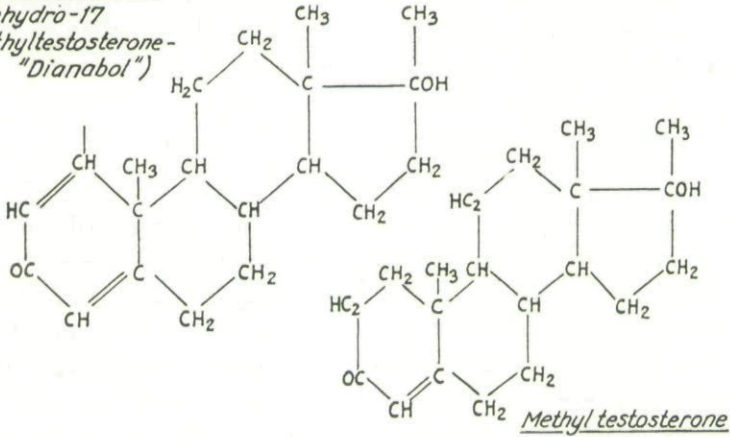


Fig. 1.

of four cases of ulcerative colitis showed a very satisfactory gain in weight, as did three cases of chronic asthma associated with recurrent attacks of bronchitis. Virilizing effects were negligible or absent.

It was, therefore, decided to study the effect administering Methandienone concurrently with corticosteroids in a selected series of cases already receiving long-term steroid therapy. Used in this way, it seemed likely that Methandienone would prove a useful adjuvant in corticosteroid therapy and might well reverse the negative nitrogen balance which inevitably tends to accompany long-term corticosteroid therapy, and at the same time, serve to check the osteoporosis and muscle wasting which so frequently develop. Muscle weakness and overt muscle wasting has been increasingly reported as a result of corticosteroid administration, and whilst this effect is perhaps most noticeable with Triamcinolone, it appears to occur with most corticosteroid preparations (Dubois 1958; Williams 1959).

The ideal anabolic agent should retain the proteogenic effects of testosterone, but should not exhibit any virilizing or progestational action, and at the same time it should not induce water or salt retention nor exert any toxic effect on the liver.

Pharmacologically Methandienone appears to meet these requirements (*Dessaulles et al.* 1959) and preliminary clinical trials tend to confirm this impression (*Wynn & Landon* 1961).

SELECTION OF CASES

Methandienone has now been studied over a period of twelve to eighteen months in a series of twenty cases of allergic asthma, already undergoing long-term corticosteroid therapy. Selection of cases was confined to those who had already commenced steroid therapy on account of the severity and intractable nature of their asthma, and limited to patients whose weight was subnormal and had been stationary or declining for a period of six months (or three months for some of the children). The majority of patients in this series were undergoing some form of specific desensitisation programme in addition to corticosteroid treatment, and all were maintained on the minimum effective dose of cortisone or equivalent preparation.

With the exception of a few patients treated in the initial

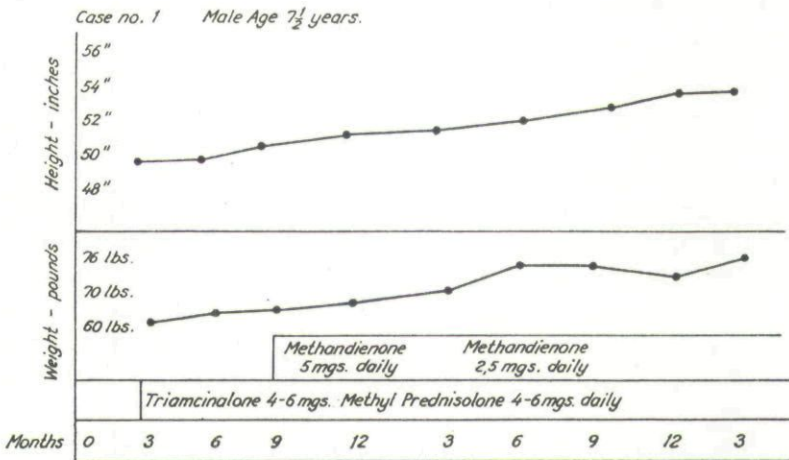


Fig. 2 a.

Showing Typical Gain in Weight and Height in Two Children treated with Methandienone and Corticosteroids.

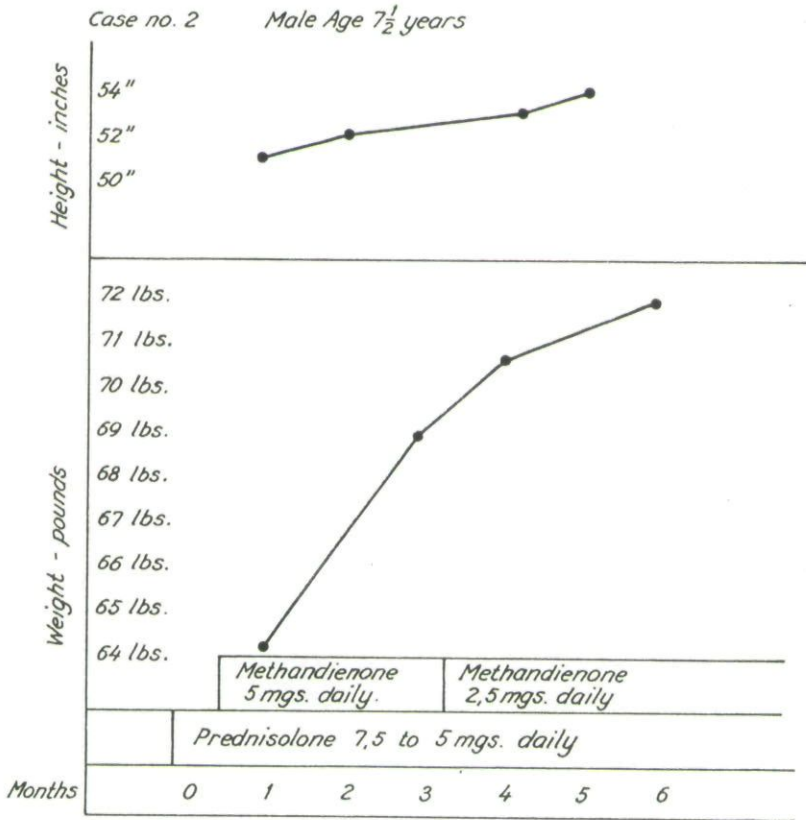


Fig. 2 b.

phases of this study with Triamcinolone (later replaced by Prednisolone or Betamethasone), all cases received Prednisolone, Methyl Prednisolone or Betamethasone in a basic daily dosage of 5–7.5 mgs. Prednisolone (or equivalent doses of the other steroids). This dosage was temporarily increased during seasonal exacerbations in the asthma or during any episode of febrile bronchitis or other upper respiratory infection.

Although in earlier studies of the drug in metabolic disease and malabsorption syndromes, a larger daily dose of 0.25–0.5 mgs. Methandienone per kilo body weight had been employed (Evans 1960; V. Wynn: personal communication), experience showed that a comparable result could be achieved with a

TABLE I
*Showing Increase in Weight and Height in Six Asthmatic Children (Aged 7-11 Years)
 Treated with Methandienone and Corticosteroids.*

Case no.	Sex	Age (years)	Diagnosis	At onset of treatment		Increase in weight/height				Androgenic effects
				Wt. (lbs)	Ht. (inches)	6 months treatment		12 months treatment		
						Wt.	Ht.	Wt.	Ht.	
1	M	8	Asthma Allergic Rhinitis & Eczema	49 3/4	61	7	1 3/4	10	3	0
2	M	7	Asthma Eczema	51	63	7	1 3/4	11	3	0
3	F	7	Asthma	49 1/2	60	7	2	14	3	0
4	M	10	Asthma	51 1/2	54	6	1 1/2	7 1/2	1 3/4	0
5	M	10	Asthma Eczema	55	66	12	2	12	2 3/4	0
6	F	10	Asthma Recurrent Bronchitis	57 1/2	79	11	1	15	1 1/2	0
Average										
8 +						8 1/3	1 1/2	11 1/2	2 1/2	Normal Menarche 11 +

smaller dose of 0.1–0.25 mgs. Methandienone per kilo body weight daily. This lower dosage appeared preferable for children and adolescents; the drug was administered twice daily for three successive weeks of every four weeks. It was hoped in this way, by omitting the drug every fourth week, there would be reduced risk of progestational effects and of gonadotrophin-inhibitory action.

In the age groups 7–11 years, there was a total number of six cases; the average gain in weight over a six months period on Methandienone was $8\frac{1}{3}$ rd lbs. with a corresponding increase in height of $1\frac{1}{2}$ inches. At the end of twelve months treatment these figures averaged $11\frac{1}{2}$ lbs. and $2\frac{1}{2}$ inches. These patients (Table I) are being maintained on small doses of Methandienone, the dose being reduced proportionately to any reduction in the dose of cortico-steroids.

Case No. 6 (J.M.) has now completed her desensitisation

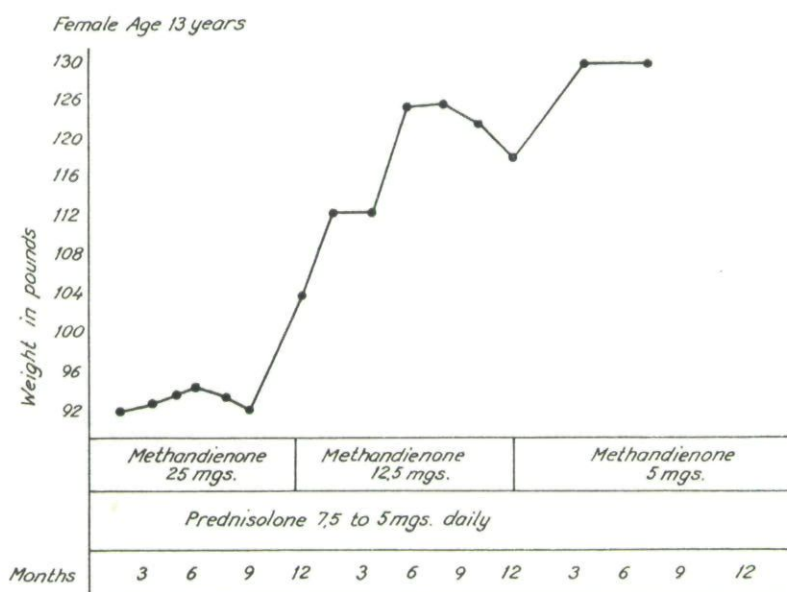


Fig. 3.

Illustrating the effect of larger doses of Methandienone (used in earlier trials) producing rapid gain in weight.

TABLE II
*Showing Increase in Weight and Height in Six Asthmatic Juveniles (Aged 12-16 Years)
 Treated with Methandienone and Corticosteroids.*

Case no.	Sex	Age	Diagnosis	At onset of treatment		Increase in weight/height				Androgenic effects			
				Wt. (lbs)	Ht. (inches)	After 6 months		After 12 months		Hirsu- tites	Acne	Ext. geni- talia	Voice
						Wt.	Ht.	Wt.	Ht.				
7	M	12	Asthma	50	53	21	1/2"	23	1"	+	0	N	N
8	F	12	Asthma	76	52	7	1 1/2"	10	2 1/2"	Sl.	0	-	N
9	F	15	Asthma Eczema	92	63 1/2	4	-	3	1 1/2"	0	0	-	N
10	F	16	Asthma Infantile Eczema	78	60	9	-	16 1/2	-	0	0	-	N
11	F	15	Asthma Eczema	110	65 1/2	9	-	14	1"	0	Sl.	-	N
12	F	13	Allergic	94	65	6	1 1/2"	27	2 3/4"	Sl.	Sl.	-	N

Supp.
2/12 ther
normal.

Reg.

Reg.

Reg.

programme; both Prednisolone and Methandienone have been withdrawn for four months and so far she has avoided any severe attacks of asthma. No virilising effects have been noted in this group; no signs of hirsuties appeared nor was there any change in voice, and growth and development of external genitalia proceeded normally.

There was a similar increase in weight noted in six patients in the age group 12-17 years. Moreover the weight increase appeared to be uniformly distributed over the body, without any tendency for increased deposition of subcutaneous fat over the hips and shoulders as so often occurs with corticosteroid therapy. Expressed in its simplest terms, it appeared to be increased muscle bulk rather than fat or fluid which largely contributed to the gain in weight. Table II shows that in this group also, such side effects as occurred from Methandienone were minimal. Case No. 10 had suppression of the menstrual periods for two months when the dose of Methandienone had been temporarily increased to 10 mgs. daily; normal rhythm returned and was subsequently maintained when the daily dose of Methandienone was reduced to 5 mgs. Cases 8, 9, 11 and 12 maintained normal and regular menstrual rhythm throughout their treatment. On two patients (Case 11 and Case 12), mild acne was noted at one stage during therapy, but this subsided without requiring local treatment and without alteration in the dose of Methandienone. It may have been a result of the corticosteroid therapy, and not necessarily a side effect from Methandienone. (Table II).

The only other side effect noted was the development of slight hirsuties on the upper lips of two girls (Cases 8 and 12); it is interesting to note that the hirsuties had almost disappeared within three months of reducing their maintenance dose of corticosteroids, and without evidence of any contributory "beauty treatment" by the patients themselves.

It seems probable, therefore, that this was a corticosteroid effect, rather than due to any virilising action of Methandienone. Increased appetite was invariably noted by all patients in this group, becoming apparent within 5-10 days of com-

TABLE III
Showing Gain in Weight in Eight Asthmatics (Originally Treated on Corticosteroids)
Following Concurrent Administration of Methandienone and Corticosteroids.

Case no.	Sex	Age	Diagnosis	Before treatment with methandienone		Gain in weight on methandienone		Virilising effects					Re- marks
				Wt. lbs.	Weight loss on cortico-steroids	6 months	12 months	Hirsu- ties	Acne	Ext. geni- talia	Voice	Menses	
13	F	29	Asthma	106	6 lbs.	6 lbs.	8½ lbs.	0	-	N	N	Reg.	
14	F	46	Asthma	103	9 lbs.	12 lbs.	15½ lbs.	Sl.	-	N	N	Reg.	
15	F	54	Asthma Hay Fever	160		3 lbs.	4 lbs.	Sl.	-	-	N	Reg.	Ø
16	F	47	Asthma	102	9 lbs.	4½ lbs.	11 lbs.	0	-	-	N	Reg. to	
17	F	36	Asthma	104		11 lbs.	16½ lbs.	0	-	-	N	Reg. Menopause	
18	M	23	Asthma + Sarcoidosis	144		4 lbs.	4 lbs.	0	-	N	N	-	X
19	M	26	Asthma Hay Fever	159		6½ lbs.	9 lbs.	0	-	N	N	-	
20	M	26	Asthma Spont. Pneumothorax	120		2½ lbs.	2 lbs.	0	-	N	N	-	

Ø Case No. 15 - Osteroporsis with root pain D8/9 relieved on Methandienone.

X Case No. 18 - 19-Nor-Androstenedione for twelve months (to Dec. 1959).

mening treatment; treatment did not interfere with normal development of breasts and the normal female body configuration was maintained. Female patients were not directly examined for changes in the external genitalia, but when questioned about this, neither the girls themselves nor their mothers had noted any changes from the normal.

In eight patients comprising the adult cases in this series, the average gain in weight was approximately 6 lbs. in the first six months with no further appreciable gain in weight over the succeeding six months. Two cases showed a loss in weight; case No. 18 had already regained 17 lbs. of his earlier loss of weight whilst on 19-nor-androstenolone prior to starting Methandienone, and the recent fall in weight coincides with active sarcoidosis. Case No. 20 also shows a recent loss of weight, but the explanation of this probably lies in water-retention whilst on Dexamethasone, for the weight dropped during ten weeks after substituting Prednisolone for Dexamethasone. (Table III).

In two cases who had been on continuous low dosage corticosteroid therapy for two or more years from their own Practitioners, two have experienced quite dramatic relief from referred dorsal root pain (Cases 14 and 15) within 10–12 days of commencing Methandienone. X-rays of the dorsal spine in Case No. 15 showed definite evidence of osteoporosis, in which there was radiologically demonstrable improvement after six months on Methandienone.

In the complete absence of any undesirable side-effects from Methandienone in this group of adult case, it is proposed to retain all patients on Methandienone so long as they continue to require regular low-dosage corticosteroid therapy. It is to be hoped that more extensive follow-up studies in those cases exhibiting osteoporosis from corticosteroid therapy may afford more definite evidence that this effect can be, at least, partially reversed with Methandienone; the mechanism of this action is not fully understood at present although there is evidence that Methandienone reduces the urinary excretion of calcium and also causes a fall in the faecal calcium too.

DISCUSSION

Methandienone has proved to be both an interesting and invaluable anabolic steroid. It exhibits an impressive anabolic effect in nitrogen balance studies (*Wynn et al.* 1961), and appears to be virtually free from any serious androgenic effects when administered in moderate doses even over a prolonged period of time. Stimulation of the appetite in children and adolescents who were underweight was particularly noticeable, accompanied in some cases by a feeling of "well being". Gain in weight may well be indirectly related to increased appetite. Another notable effect was the disappearance of lassitude and early muscle fatigue which many patients had previously noted whilst on corticosteroids; this effect does not appear to be psychological but rather to be directly associated with the positive nitrogen balance attained on Methandienone.

It had been expected that some virilising effects might be noticed with a testosterone derivative, but experience showed these effects did not occur. In those few cases developing acne or hirsuties, it seemed likely that these effects resulted from the concurrent corticosteroid therapy rather than from Methandienone. No significant suppression of menstruation was noted, nor were any progestational effects found.

In children and adolescents the drug showed a definite action in stimulating growth, both in the younger (7-11 years) age group and in the puberty (12-17 years) group; this effect appears to be related to its anabolic activity. Moreover, in those patients who have completed their treatment with corticosteroids and Methandienone, growth has continued; it is unlikely, therefore, that the drug accelerates closure of the epiphyses. No hepatotoxic action was noted; one case (No. 18) whose turbidity tests were abnormally raised when Methandienone treatment commenced showed improvement and return to normal turbidity values whilst on the drug. Water and salt retention did not occur; on the contrary Methandienone appeared to assist in reducing water and salt retention which had already developed with corticosteroid therapy in two cases (Cases 7 and 20).

SUMMARY

The use of Methandienone as an adjuvant to corticosteroids has been studied over the past two years in a series of twenty asthmatics already receiving long-term steroid therapy.

It has been shown to be an effective anabolic agent, reducing or correcting the chronic protein loss which so often accompanies corticosteroid therapy. Moreover this anabolic effect can be attained with small doses (0.1–0.25 mg. Methandienone per kilo body weight) that are free from virilising side effects. Salt-retention and hepatotoxic effects were not observed.

Methandienone has been shown to stimulate growth in children. It is, as yet, too early to judge its efficacy in reversing osteoporotic changes resulting from prolonged corticosteroid treatment, but it appears to exert some useful therapeutic effect in this direction which merits further study.

ACKNOWLEDGEMENTS

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