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Oral Testosterone, a Reappraisal

P.R. Daggett, M.J. Wheeler and J.D.N. Nabarro

Cobbold Laboratories, Sir Jules Thorn Institute of Clinical Science, Middlesex Hospital, and Department of Chemical Pathology, St. Thomas' Hospital, London

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Abstract. A microparticulate form of free testosterone was given orally to 6 hypogonadal men. Plasma levels were followed after a 200-mg dose, and a double-peak effect was observed. This suggests that particles of different sizes were absorbed at different rates. The clinical and biochemical effects were observed over a 2-month period, on a dose of 200 mg twice daily, taken in place of the usual androgen replacement. The results indicate that absorption is not sufficiently reliable for routine use. The large doses required to achieve therapeutic levels, make oral administration of free testosterone impractical.

Introduction

Since the report by *Foss* (1) in 1939, free testosterone has been considered to be ineffective when given orally, owing to a combination of poor intestinal absorption and rapid hepatic metabolism (2, 3). It has accordingly been necessary to administer androgens for replacement therapy by an alternative means, including sublingual methyltestosterone, injected testosterone esters, implanted free testosterone and oral testosterone analogs such as fluoxymesterone (4). Some of these have disadvantages, and interest has recently returned to the oral route for free testosterone, in the form of very small (micronized) particles (5, 6). We have treated 6 hypogonadal males with such a preparation for 2 months, and report here our results.

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Patients and Methods

Informed consent was obtained from 6 male patients with androgen deficiency caused by primary testicular disease in 3 and deficiency of pituitary gonadotrophic hormones in the others. All had been treated with androgens for 1–6 years, but medication was withdrawn 30 days before commencing this study. On the first day, an oral absorption test was carried out. Each patient was fasted overnight but was allowed free fluids. An indwelling catheter was inserted into a forearm vein under local anesthesia, and its patency was maintained by flushing intermittently with a solution containing 250 U heparin/ml. A basal sample was taken after 30 min, and a tablet containing 200 mg of micronized free testosterone was administered orally. Samples of blood were then taken at hourly intervals for 8 h. Each sample was divided into two, 10 ml being heparinized for testosterone measurement, and 10 ml being allowed to clot for measurement of prolactin and gonadotrophins. After immediate centrifugation at 2,500 rpm for 10 min, plasma and serum were stored at – 20 °C while awaiting analysis.

Subsequently, the patients took 200 mg free testosterone twice daily, at 08.00 and 20.00. They attended weekly, 2 h after ingestion and on the same day of the week, for blood samples to be taken. Treatment was continued for 8 weeks, and frequency of erections, shaving and feeling of well-being were recorded. Tests of liver function were made before starting therapy and at the end of the course (bilirubin, alkaline phosphatase, aspartate aminotransferase, albumin and total protein were measured on a Vickers M 300 autoanalyzer).

Testosterone assay. An antibody-coated tube radioimmunoassay was used, with testosterone-3-^{125}I-histamine as ligand (7). Antiserum was raised in New Zealand white rabbits to testosterone-3-human albumin. This has a cross-reaction with 5-α-dihydrotestosterone of 25%, and with DHEA, androsterone and androstenedione of 0.1%. The intra-assay coefficient of variation (C of V) is 4.5%, and inter-assay C of V 11.5%.

Prolactin assay. A double-antibody method was employed, using VLS-1 as standard. This system has an intra-assay C of V of 4% and an inter-assay C of V of 6.9%.

Luteinizing hormone (LH) assay. A double-antibody method was employed, using MRC 68/40 as standards. The intra-assay C of V is 2% and the inter-assay C of V 11%.

Follicle stimulating hormone (FSH) assay. A double-antibody method was employed, using MRC 69/104 as standards. The intra-assay C of V is 2% and the inter-assay C of V 12%.

All the samples over the 2-month period from any one patient were measured in the same assay.

Results

General

There was no deterioration in liver function in any patient, during the course of treatment. Subjective impressions are recorded in table I, but there was no correlation between these and the plasma testosterone levels.

Table I. Clinical details of the 6 patients

Patient	Age	Clinical details	Shaving frequency	Potency	General wellbeing	Duration of androgen therapy (years)
1	27	hypogonadotrophic hypogonadism (idiopathic)	no change	no change	no change	3
2	44	right testis atrophic after herniorrhaphy, left orchidectomy for seminoma	no change	no change	no change	2
3	55	hypophysectomy for chromophobe adenoma in 1964	no change	no change	no change	6
4	17	testes atrophic after bilateral non-descent	increase	increase	improved	1
5	46	Klinefelter's syndrome	no change	increase	improved	6
6	50	hypogonadotrophic hypogonadism with anosmia	increase	no change	improved	4

Plasma Testosterone

The results of the oral absorption tests are shown in figures 1 and 2. All patients had initial plasma testosterone levels below the lower limit of normal for an adult male (9 nmol/l). An increase in plasma testosterone occurred in all patients but in 2 it failed to rise to the normal range (9–24 nmol/l) during the absorption study. In all cases, there was a fall from the initial peak of plasma testosterone, followed by a secondary rise at about 7 h after ingestion of the 200-mg tablet. In 4 of 6 patients, levels during prolonged treatment showed an upward trend, so that higher values were found at the end of the 2 months than had been achieved at the peak of the absorption study. (Value D in table II is the mean of the last three values obtained.) The 2 patients in whom this phenomenon was not observed, had the highest initial levels of plasma testosterone. There was no difference between subjects with primary and secondary hypogonadism at any stage.

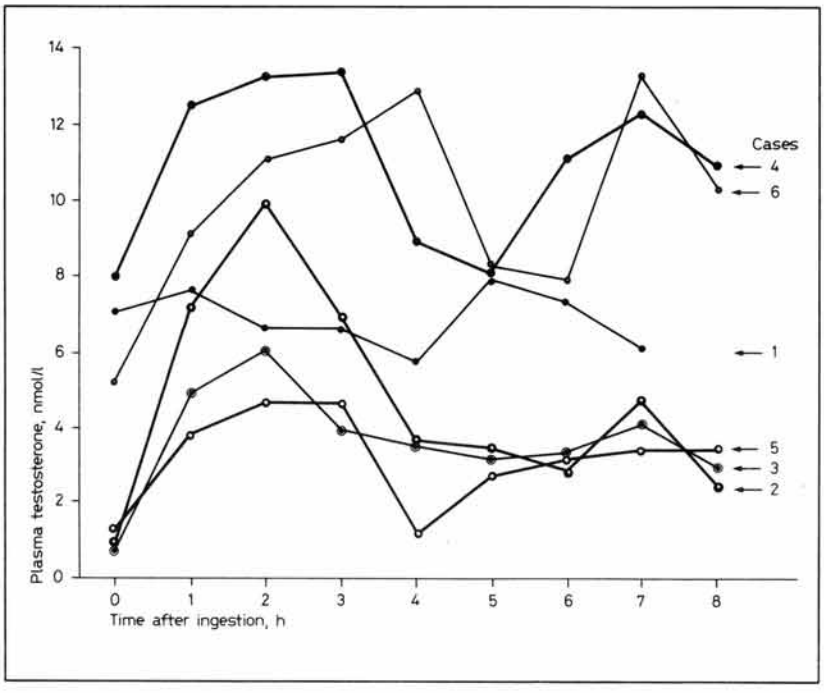

Fig. 1. Plasma testosterone levels in the 6 subjects, at hourly intervals after a single dose.

Plasma Prolactin and Gonadotrophins

Plasma prolactin levels were normal is 5 of 6 studies and showed no change at any time. In case 4, prolactin level had risen at the end of the study, and was then above the upper limit of normal (15 μg/l). Plasma gonadotrophins were elevated in the 3 patients with primary gonadal failure and low in the 3 with hypothalamic-pituitary disease. They showed no changes during the course of this study.

Discussion

The daily production of testosterone by the normal adult male lies between 3.5 and 11.8 mg, with a mean of 6.5 mg (8), and the dose used in this study was thus in the region of 50 times the physiological requirement. Since the plasma

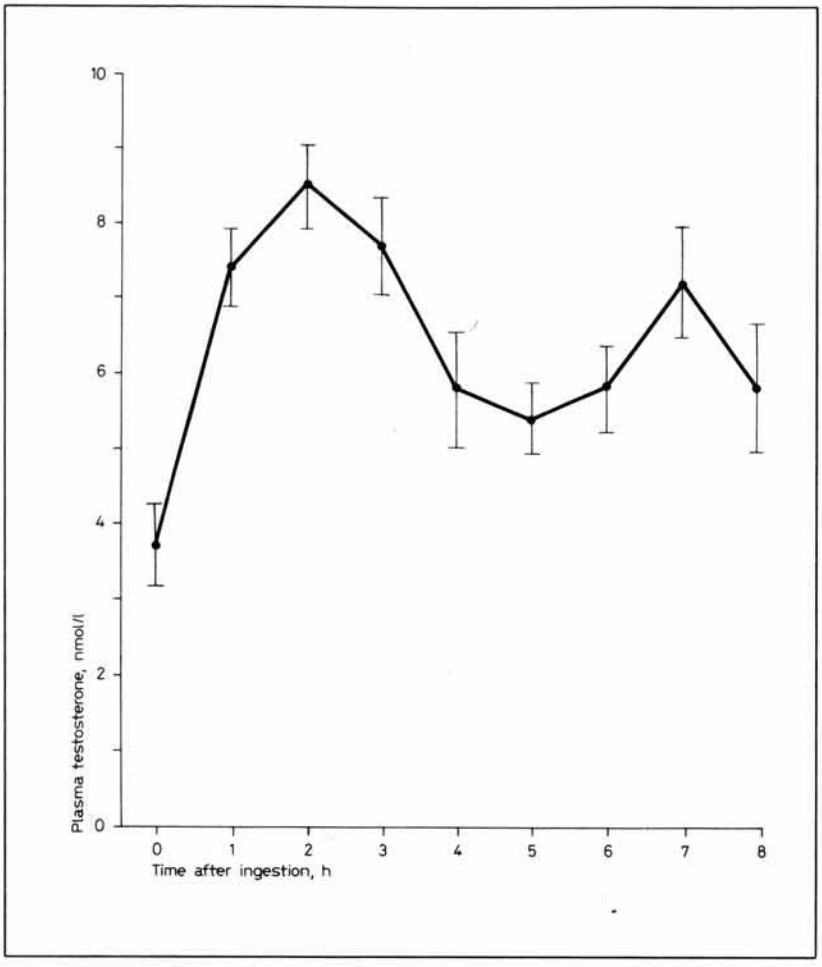

Fig. 2. Mean plasma testosterone ± SEM, at hourly intervals after a single dose.

levels achieved were below or in the lower part of the normal range, a considerable part of the ingested dose must be judged to have been ineffective. *Nieschlag et al.* (5) found that 63 mg free testosterone given daily to men with normal gonadal function, provided inadequate plasma levels and recommended the use of testosterone undecanoate in arachis oil, in its place. *Johnsen et al.* (6), on the other hand, considered that 400 mg free testosterone daily, restored the plasma levels of 4 hypogonadal males to acceptably normal levels and advised

Table II. Details of hormonal levels at various stages of the study

Patient		Testosterone nmol/l	Prolactin μg/l	FSH U/l	LH U/l
1	A	6.8	4.8	<0.3	3
	B	7.5	4.8	<0.3	3
	C	5.6	5.4	<0.3	<1
	D	5.4	5.5	<0.3	<1
2	A	0.8	6.5	>20	52
	B	9.6	6.8	>20	45
	C	4.4	5.9	>20	62
	D	12.2	8.0	>20	48
3	A	0.6	4.6	1.8	10
	B	5.9	3.8	1.3	8
	C	2.8	5.6	1.8	9
	D	10.7	5.0	1.6	7
4	A	7.7	8.6	>25	57
	B	13.4	7.3	>25	50
	C	10.5	13.5	>25	57
	D	7.8	17.2	>25	54
5	A	2	4.3	22	25
	B	4.5	4.4	22	19
	C	7.5	4.3	21	19
	D	8.0	4.6	20	22
6	A	5.0	4.8	<0.3	2
	B	13.0	3.9	<0.3	3
	C	16.0	5.0	<0.3	4
	D	16.0	4.2	<0.3	2

A = Initial level, before any medication; B = level at first peak during absorption test; C = level after 1 week of treatment with 400 mg free testosterone daily; D = level at the end of 8 week treatment.

the use of this preparation routinely. Our findings indicate that in 3 of 6 patients, a single oral dose of 200 mg free testosterone gave inadequate plasma levels. In the other 3, plasma levels rose to within the normal range 3 h after ingestion, but fell to below normal again by 4 h after ingestion. The findings of *Johnsen et al.* (6) suggested a longer duration of action than this, with a plasma half-life of 5–7 h, though this was surprising in view of the rapid turnover of

testosterone in blood (9). The explanation may be that a different particle size was used in the preparation used in their study than in ours, as this might be expected to influence the rate of absorption. In this context, the secondary rise of plasma testosterone levels seen in all of our patients, is of interest. It was also observed (though not commented on) in the studies of *Johnsen et al.* (6) and may be caused by differential absorption of two 'families' of testosterone particles of differing size. The variation in the particle size of testosterone in tablet form, was noted by *Johnsen et al.* (6). Profiles of particle size are not available for the preparation used in our study, but some variation is very likely. Larger particles would be absorbed more slowly, and if there were two groups of particles, early and late absorption peaks might therefore be expected.

The rise of plasma testosterone over the 2 months of therapy in 4 of our patients was surprising. An effect of sex hormone binding globulin (SHBG) seems unlikely, as administration of testosterone would be expected to reduce the plasma level of SHBG (10), and therefore the measured testosterone would fall. Alternative explanations could be an enhancement of absorption from the gut, or reduced metabolism, although the latter is also unlikely, as the metabolic clearance rate of testosterone increases with the plasma concentration (9). In cases 1 and 4, an increase in plasma testosterone concentration between the peak of the absorption study and the end of the 2-month treatment period (levels B and D in table II) was not observed. In these two cases, the initial plasma testosterone concentrations were the highest of the group of 6 patients. The failure of the plasma level to rise could hence be caused by induction of androgen metabolizing enzymes, by the orally administered testosterone, as discussed by *Nieschlag et al.* (11). Although the antiserum used in our testosterone assay has a 25% cross-reaction with 5-α-dihydrotestosterone, it is unlikely that important errors were introduced. The normal circulating level of this steroid is around 2 nmol/l, and so it unlikely that more than 0.5 nmol/l of the measured testosterone could have been caused by this cross-reaction (7). Similarly, cross-reaction with other androgens would be negligible.

Plasma prolactin levels fluctuated little and the elevation seen in case 4 may be a consequence of the periodic variations of plasma prolactin, which are known to occur (12). Thus, blood samples may have been obtained during a burst of prolactin release, thereby giving a misleadingly high result. Plasma testosterone levels did not have any effect upon gonadotrophin levels in those patients with primary testicular disease. This was probably because plasma testosterone levels had not been raised sufficiently to inhibit pituitary gonadotrophin production.

From the data in this and other published studies, it may be concluded that free testosterone is absorbed when given orally in vastly supra-physiological doses. In some patients, plasma testosterone levels may reach the normal range, but in others, they will be inadequate. Patients likely to benefit can only be identified by repeated estimations of plasma testosterone and therefore, this form of treatment is unsuitable for routine use. In addition, the large total daily dose required would be uneconomical, in these times when the raw materials for steroid production are becoming more limited. Oral free testosterone therapy cannot therefore be recommended.

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Dr. *Peter Daggett*, Department of Medicine and Endocrinology, Central Middlesex Hospital, Acton Lane, *London NW10 7NS* (England)