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Bioavailability of Oral Testosterone in Males

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Summary. Twenty-six male volunteers received a single oral dose of testosterone as free crystals or as the undecanoate ester. The latter was given either in crystalline form or in arachis oil. All preparations were tested three times in the same individual, whilst fasting on 2 days and on one day together with a breakfast rich in fat. Serum testosterone concentration was measured at intervals for up to 6–24 h after the dose. A significant and reproducible rise in serum testosterone level was found after ingestion of free testosterone. Testosterone esterified with undecylenic acid was only effective when administered in arachis oil. The meal increased the bioavailability of the ester, but had hardly any effect on that of the free hormone. It is concluded that bioavailability of oral testosterone can be improved by pharmaceutical means to an extent sufficient to produce adequate blood levels in substitution therapy.

Key words: testosterone, testosterone undecanoate, arachis oil; serum level, oral administration

Alternatives to parenteral administration of testosterone are suppositories [1, 2] and oral testosterone, either in free form [3], or as the undecanoate ester [4]. Oral administration has received increasing interest during the last few years. The purpose of the present investigation was to evaluate the extent to which bioavailability of oral testosterone was influenced by esterification with undecylenic acid, administration of the ester in crystalline form or dissolved in arachis oil, and by simultaneous ingestion of a fat rich meal.

Material and Methods

26 male inpatients volunteered for the investigation. Except for 3 with hypogonadism (Experiment 4), they were all convalescing from diseases not affecting the endocrine, renal or gastrointestinal systems, mainly myocardial infarction.

Experiment 1. 6 men, mean age 62 years and mean serum testosterone concentration 20.2 nmol/l, were given a single dose of crystalline testosterone 100 mg in micronized form: 80% of the particles measured 2–5 microns in diameter. Blood for analysis of testosterone concentration was collected 0, 0.5, 1, 2, 4 and 6 h after ingestion of the tablet. The experiment was performed 3 times in each individual. On two of the days the patient was fasting, and on one day the tablet was taken with a breakfast of 474 kcal (= 1986 kJ), of which 59% was fat.

Experiment 2. 6 men, mean age 65 years and mean serum testosterone concentration 12.1 nmol/l, were given a single dose of crystalline testosterone undecanoate 100 mg (equivalent to 63 mg of testosterone) as a tablet. Blood for analysis of testosterone concentration was taken 0, 0.5, 1, 2, 4, 6, 12 and 24 h after ingestion of the tablet. The experiment was performed 3 times according to the protocol described above.

Experiment 3. 8 men, mean age 65 years and mean serum testosterone concentration 11.3 nmol/l, were given a single dose of testosterone undecanoate 100 mg (= 63 mg testosterone). The testosterone ester was administered in arachis oil, 5 ml containing 100 mg of the ester. Blood for analysis of testosterone concentration was collected as in Experiment 2, and for analysis of serum LH and FSH after 0, 6,

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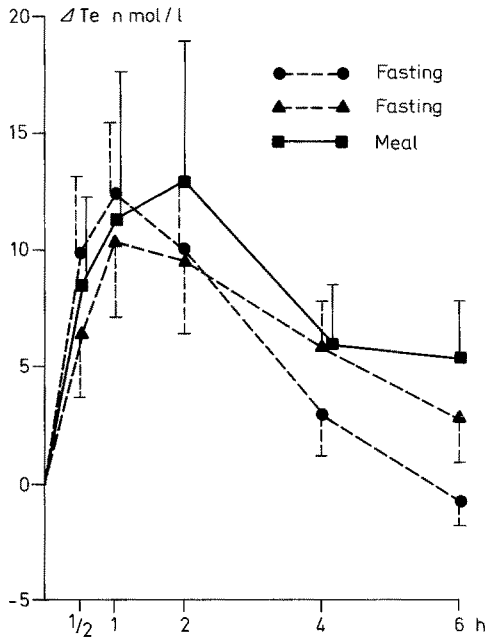

Fig. 1. Mean increment in serum testosterone concentration (△ Te) after oral administration of micronized free testosterone 100 mg to 6 males. The testosterone was given one day with a fat-rich breakfast, and on the two other days with the patient fasting. Vertical line indicate 1 SEM in all figures

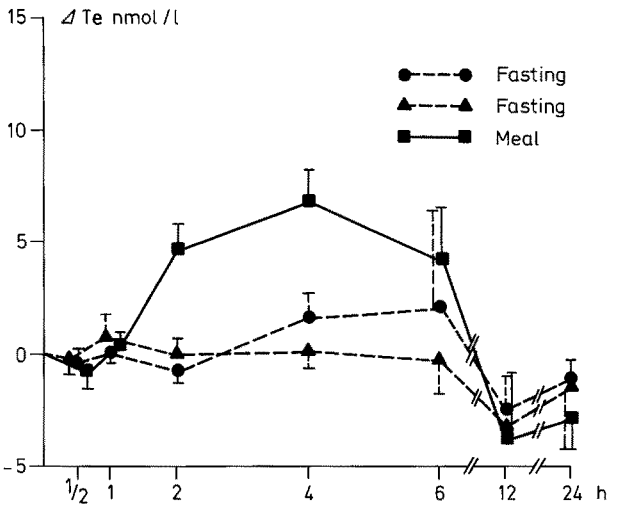

Fig. 2. Mean increment in serum testosterone concentration (△ Te) after oral administration of testosterone undecanoate 100 mg (= 63 mg Te) as tablets to 6 males. Breakfast and fasting as in Figure 1

12 and 24 h. The experiment was performed 3 times according to the protocol described above.

Experiment 4. 6 males, mean age 49 years of whom 3 suffered from hypogonadism, were given testosterone undecanoate 100 mg (= 63 mg testosterone) on two separate days, on both occasions fasting. On the first day the dose was given as tablets of the crystalline form, and on the second day it was dissolved in arachis oil 5 ml as in Expt. 3. Blood for analysis of testosterone concentration was drawn after 0, 1, 2, 4 and 6 h.

A minimum of 48 h separated all experimental days. Some of the patients also received anticoagulant therapy and in them the drug regimen was kept unchanged during the period of the investigation.

Testosterone [5] and LH and FSH [6] in serum were determined by radio-immuno-assay. The testosterone method included paper chromatography before the assay.

Results

Experiment 1. The mean increase in serum testosterone concentration above basal level after oral ingestion of crystalline micronized testosterone 100 mg is shown in Figure 1. On all days the peak concentration was reached after 1–2 h, with return almost to basal level after 6 h.

The areas under the curves in Figure 1 calculated by the trapezoidal rule, are compared in Figure 4 A. The difference in total testosterone concentration on the two fasting days was very small, the area on Day 2 being 102% of that on Day 1. A fat-rich breakfast increased this area to 142%, but the difference from Day 1 was not statistically significant (Student's t-test for paired comparison). Thus it appears that the preparation tested could increase serum testosterone concentration, but the increase after the dose of 100 mg was rather small and of short duration. Results were reproducible in the fasting state, and a meal did not definitely enhance bioavailability.

Experiment 2. Fasting ingestion of testosterone 63 mg as the crystalline undecanoate ester had no apparent effect on serum testosterone concentration (Figs. 2, 4B), but an effect was observed when the same dose was given with the standard meal ($p < 0.01$).

Experiment 3. The mean increase in serum testosterone in 8 males on 3 separate days after oral ingestion of testosterone undecanoate 100 mg in arachis oil (= 63 mg testosterone) is shown in Figure 3. The curves are similar to those in Figure 1, but the peak

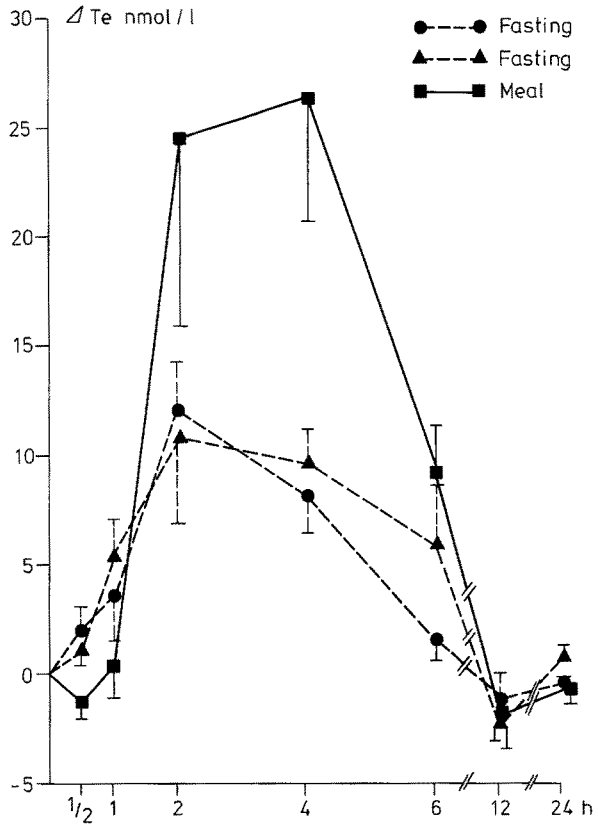

Fig. 3. Mean increment in serum testosterone concentration (△ Te) after oral administration of testosterone undecanoate 100 mg (= 63 mg Te) dissolved in arachis oil to 8 males. Breakfast and fasting as in Figure 1

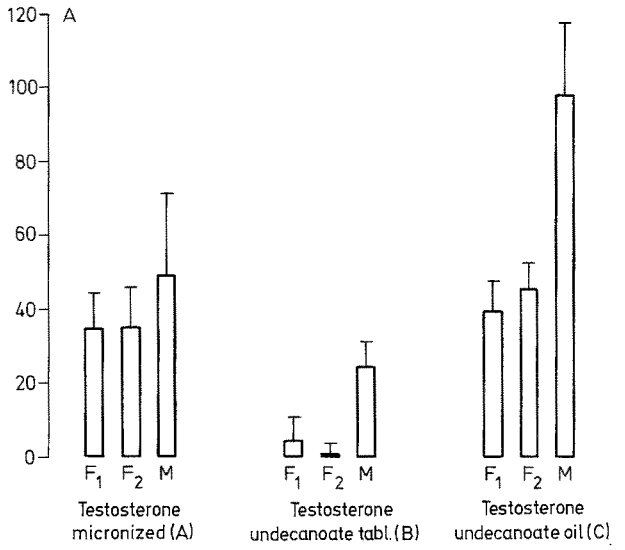

Fig. 4. Mean increment in bioavailable testosterone expressed as the area (A nmol/l × h) under the curve for the increment in serum testosterone concentration from time 0 to 6 hours. The form of testosterone administered is A) free micronized 100 mg, B) undecanoate 100 mg as tablets, (= 63 mg Te), C) undecanoate 100 mg (= 63 mg Te) dissolved in arachis oil. Bars indicate means.
F_1: 1. day of testosterone administration to fasted patient
F_2: 2. day of testosterone administration to fasted patient
M: Testosterone administration with a standard breakfast

concentration was later. The serum testosterone concentration 12 and 24 h after ingestion of the test dose was not significantly different from the value at 0 h.

In contradistinction to the result of Experiment 1, the meal increased the area under the 0–6-h curve to 247% (Fig. 4C), which is a significant rise ($p < 0.02$). The areas on the two fasting days were not significantly different (100% vs. 114%).

Testosterone undecanoate in oil in this experiment gave a larger increment in serum concentration than crystalline testosterone, when expressed as area under the curve (nmol/l × h) per mg testosterone administered in the fasting state (0.68 vs. 0.35, $p < 0.01$). Bioavailability of the hormone at this dose level appears therefore to be improved by esterification, when the preparation was administered in arachis oil, and given to a fasting subject.

LH and FSH. Serum FSH concentration showed fluctuations without a definite trend, and serum LH had a tendency to decline after 6 h. The mean values after 0, 6, 12 and 24 h and the significance of the difference from 0 h are shown in Table 1.

Experiment 4. To exclude the possibility that the increased bioavailability observed when testosterone undecanoate was administered in arachis oil was due to some difference between the two groups of individuals tested, six other patients were given both preparations on two different days. The individual results (Fig. 5) confirm the poor bioavailability of the crystalline form, and the improvement obtained by its administration in arachis oil. A greater increase in serum testosterone appears to have been produced in the three hypogonadal males, but their number was too small for any definite conclusion to be drawn.

Discussion

From these results it can be concluded that there is a significant and reproducible rise in serum testosterone concentration after oral administration of free crystalline testosterone in micronized form; this effect is barely improved by a high fat meal.

When testosterone was administered as the undecanoate ester, the serum testosterone concentration

Table 1. Serum concentration of LH and FSH after oral ingestion of testosterone undecanoate 100 mg in arachis oil on three different days. Mean ± SEM for 8 individuals. p: significance of difference from 0 h
N. S.: not significant

		Plasma LH, μg/l				Plasma FSH, μg/l			
Hour after dose		0	6	12	24	0	6	12	24
Fasted	Mean	0.91	0.55	0.68	0.71	1.22	1.27	2.10	1.32
	SEM	0.21	0.08	0.13	0.15	0.45	0.37	0.94	0.45
	p		NS	NS	<0.05		NS	NS	NS
Fasted	Mean	0.86	0.65	0.67	0.75	1.37	1.41	1.38	1.28
	SEM	0.14	0.13	0.15	0.18	0.49	0.51	0.52	0.49
	p		<0.02	<0.01	<0.05		NS	NS	NS
Fed	Mean	0.84	0.68	0.64	0.85	1.31	1.48	3.30	1.34
	SEM	0.20	0.17	0.17	0.23	0.43	0.41	0.83	0.44
	p		<0.02	0.05	NS		NS	NS	NS

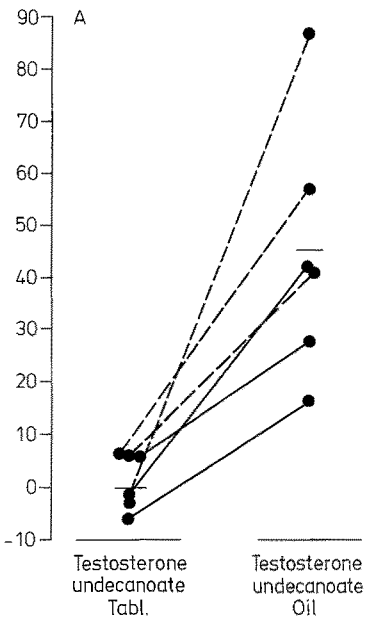

Fig. 5. Increase in bioavailable testosterone when testosterone undecanoate 100 mg (= 63 mg Te) was administered to the same fasting patient as a tablet and as a solution in arachis oil on different days. Values from the same patient are connected. Solid lines: Normal males. Dotted lines: Hypogonadal males. A: Area under the curve for the increase in serum testosterone from time 0 to 6 h (nmol/l × h)

was considerably increased when the compound was given in arachis oil, and this effect was further enhanced if the preparation were taken with a high fat meal.

The majority of the data were derived from experiments in males with normal gonadal function, whereas most prospective users of the drug will suffer from hypogonadism. Objections might be raised to the validity of sequential serum testosterone determinations, because in eugonadal males several factors are present that would tend to reduce the rise in serum level after oral treatment. First, serum testosterone concentration normally has a slight downward trend throughout the day [7, 8]. This tendency to fall might be accentuated by suppression of LH, as was indicated by our findings, which suggested a reduction in endogenous testosterone. In addition, testosterone-metabolizing liver enzymes are more active in normal males than in females and hypogonadal males [9]. If the possible combined effect of these factors is taken into consideration, the testosterone increments shown here may be regarded as minimum values.

The poor bioavailability of testosterone undecanoate in tablet form was somewhat unexpected, in view of the favourable results published by Nieschlag et al. [10]. The cause of the discrepancy is not readily apparent, although pharmaceutical factors, such as particle size and vehicle, may be of importance.

The present results, however, are in complete agreement with the finding by Nieschlag et al. of increased bioavailability of testosterone undecanoate in arachis oil [10]. The preliminary positive results of Hirschhäuser et al. [11], and of Sarris et al. [12], are also supported by our findings. Recently, Franchi et al. [13] have documented the practical value of this preparation in substitution therapy.

When given by mouth free testosterone is subject to metabolism both in the intestinal wall and in the liver. Esterification with undecylenic acid renders the molecule lipophilic. It is then to some extent protected from metabolism by the intestinal wall, and absorption directly into lymph is facilitated, whereby first-pass metabolism in the liver is reduced, as has been demonstrated both in animal experiments [4] and in humans [14]. In accordance with this view, the profound effect on bioavailability of arachis oil in experiments may be explained by formation of chylomicrons, which would facilitate passage into lymph.

The addition of a meal rich in fat probably exerts its effect through the same mechanism, although prolongation of gastric emptying in itself may have been of some importance in achievment of higher serum levels. The slight effect of the meal on serum levels after ingestion of free testosterone does suggest that the influence of the latter mechanism should not be overestimated. Irrespective of the mechanism involved, the fact that bioavailability of testosterone can be improved by esterification and administration with fat offers a prospect for development of even better combinations of esters and pharmaceutical formulations. This is desirable since the dose required for satisfactory replacement therapy with testosterone undecanoate is still high – 120–240 mg [15, 16, 17].

According to Johnsen et al. [3], free testosterone in micronized form also gives a satisfactory serum level, and in fact Føgh et al. [18] demonstrated that even larger crystals may sometimes be effective. The present results with micronized free testosterone support these findings, but large doses were necessary. This may be considered objectionable for at least two reasons. First, liver function may be adversely affected by a large load of steroid during its first passage through the liver, although clinical experience so far seems to refute this possibility [19]. We have treated 5 hypogonadal men orally with free testosterone 400 mg per day for 1 to 3 years, the total dose consumed amounting to an average of 305 g (144–432 g) per patient. All biochemical liver function tests, including bromsulfalein retention, were normal, and so were liver scintigrams and liver biopsies. However, with the life-long nature of the therapy in mind, the period of observation still is quite short. Continuous ingestion of testosterone may also lead to enzyme induction in the liver, resulting in increased metabolic breakdown of the hormone itself [20, 9]. This effect might be reduced if the "first-pass" load on the liver could be lowered by a suitable mode of administration.

In conclusion, bioavailability of oral testosterone may be so improved by several means that this mode of administration may become useful in practice, but the large doses still required warrant caution concerning possible long-term side effects. When lipophilic testosterone esters are used, they should be administered in oily solution and with meals.

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