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Bioavailability and LH-Suppressing Effect of Different Testosterone Preparations in Normal and Hypogonadal Men[1]

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Abstract. The therapeutic effectiveness of intramuscularly administered testosterone esters and free testosterone in suppositories was investigated by the measurement of plasma testosterone and LH levels after administration to normal and hypogonadal men. Testosterone levels were elevated above the lower physiological limit for 1 day after 25 mg testosterone propionate, for 2 days after 50 mg testosterone propionate and for 14 days after 250 mg testosterone oenanthate. LH levels were suppressed for the corresponding periods. Elevated plasma testosterone and suppressed LH levels were maintained by testosterone suppositories (3 × 20 mg for 5 days).

Introduction

Free unesterified testosterone, administered orally, theoretically the first choice as substitution therapy in cases of androgen deficiency, is ineffective since it is readily metabolized in the liver after absorption via the portal vein (*Foss,* 1939; *Nieschlag et al.*, 1975). For this reason free testosterone must be administered either rectally (*Hamburger,* 1958) or parenterally (*Heller and Maddock,* 1947) if it is to be effective. Esterification of the testosterone molecule at position 17, e.g., with propionic or oenanthaic acid, prolongs the activity of testosterone in proportion to the length of the side chain when administered intramuscularly.

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Testosterone esters given by injection as well as free testosterone in suppository form have been applied clinically for many years. However, dosage and frequency of administration are still predominantly determined by clinical experience and 17-ketosteroid excretion (*Hamburger,* 1956, 1958; *Diczfalusy and Cassmer,* 1961; *Heller and Maddock,* 1947). There have been very few published reports on plasma testosterone levels after application of the several testosterone preparations in various clinical disorders. The data from female transexualists (*Aakvaag and Vogt,* 1969) cannot be representative for male subjects. Studies on the use of testosterone esters in therapy have not included an objective parameter for assessing the effectiveness of the preparations used (*Coppage and Cooner,* 1965; *Vermeulen,* 1973) or are also based on infrequent sampling (*Kley et al.,* 1973).

We have therefore systematically investigated the effects of testosterone propionate (at two different dose levels), testosterone oenanthate and free testosterone in suppository form on plasma testosterone levels in normal and hypogonadal men. LH was measured simultaneously to evaluate the effectiveness of the therapy.

Subjects and Methods

Altogether 32 men were investigated, grouped as described below. Hospitalized men in the convalescent phase of gastrointestinal or pulmonary diseases, but free of endocrine disturbances, formed the control groups a, b, d and f. All subjects of groups a–e were injected at 18.00 on the control day. Blood samples were obtained at 8.00 on the control day and on the test days; a sample was also obtained at 18.00 from subjects in groups a and b.

Group a: Four men, age 20–45 years, received 25 mg testosterone propionate i.m.

Group b: Four men, age 33–74 years, received 50 mg testosterone propionate i.m.

Group c: Seven patients with secondary hypogonadism due to chromophobe adenomas of the pituitary, age 19–58 years, received 50 mg testosterone propionate i.m. Five patients were investigated prior, two 6 months after surgical removal of the adenoma. They had not received testosterone treatment previously. In those patients requiring replacement with thyroid or adrenal hormones, medication was continued during the course of the study.

Group d: Four men, age 24–55 years, received 250 mg testosterone oenanthate i.m.

Group e: Seven patients with primary hypogonadism, 3 castrates and 4 patients with Klinefelter's syndrome, age 20–58 years, received 250 mg testosterone oenanthate i.m. The usual androgen substitution therapy in these cases was discontinued at least 6 weeks before the present investigation.

Group f: 20 mg testosterone suppositories were administered to six men, age 39–77 years, for 5 days at 6.00, 12.00 and 17.00. Blood samples were obtained on the control day and test days 1 and 5 at 8.00, 14.00 and 19.00.

Testosterone (*Nieschlag and Loriaux,* 1972) and LH (*Franchimont,* 1968) were measured by specific radioimmunoassay in all blood samples. The testosterone esters were purchased from Schering AG, Berlin (Testoviron®); the suppositories were prepared on our request by Ferring GmbH, Kiel.

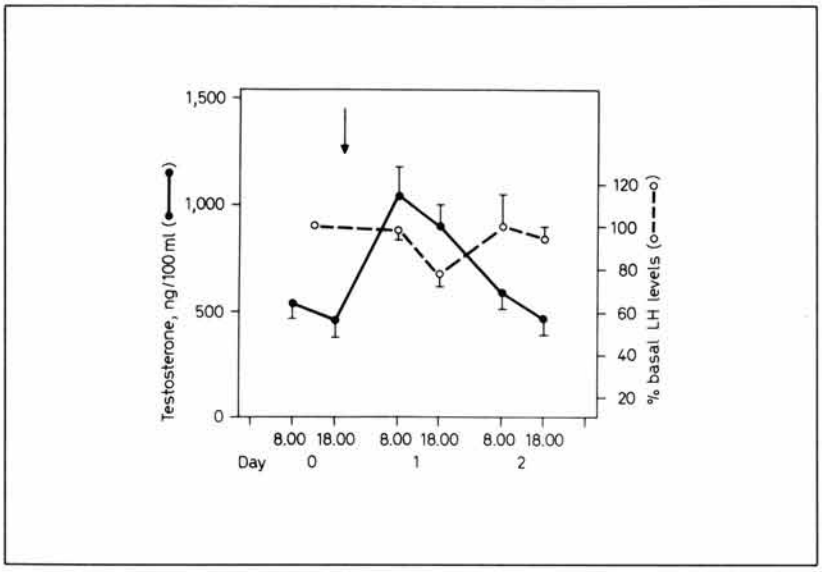

Fig. 1. Effect of 25 mg testosterone propionate on plasma testosterone and LH in four normal men. LH levels (as in fig. 2, 4 and 5) are expressed as percent change from the basal levels, which are taken as 100 %. As in the following figures, mean values ± 1 SEM are given.

Results

The results from the various groups investigated are shown in figures 1–6. With all injected preparations peak testosterone values exceeding the upper physiological range of 1,000 ng% were observed on the 1st day after administration of testosterone propionate and on the first 3 days after testosterone oenanthate. If the lower normal range is taken as 400 ng%, then levels above this range were observed in controls and in patients for 1 day after 25 mg testosterone propionate, for 2 days after 50 mg testosterone propionate, and for 14 days after 250 mg testosterone oenanthate. Following the administration of 25 mg testosterone propionate to the control subjects, LH levels were significantly suppressed on day 1 of treatment as compared to basal levels (15.0 ± 0.8 mIU/ml, mean ± 1 SEM; $p < 0.0025$). After 50 mg testosterone propionate, LH levels were suppressed to 74 % of the basal levels by the 3rd day in the control group (basal LH 14.1 ± 1.6 mIU/ml; $p < 0.05$). Following 250 mg testosterone oenanthate, LH levels in the control group were suppressed by 40 % for 10 days (basal LH 11.7 ± 1.5 mIU/ml; $p < 0.0005$). Although the LH levels in the group of hypogonadal men studied were suppressed to a similar extent, levels remained above the normal range (basal LH 37.9 mIU/ml). LH levels in the

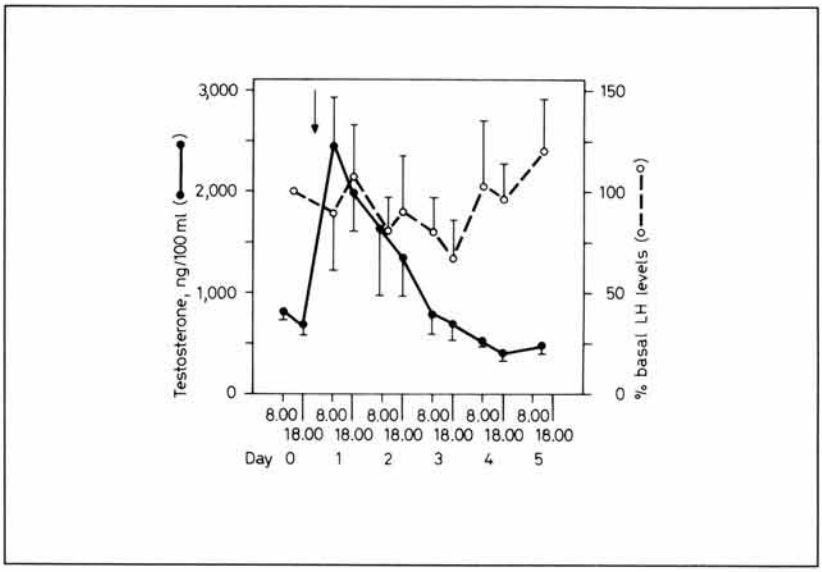

Fig. 2. Effect of 50 mg testosterone propionate on plasma testosterone and LH in four normal men.

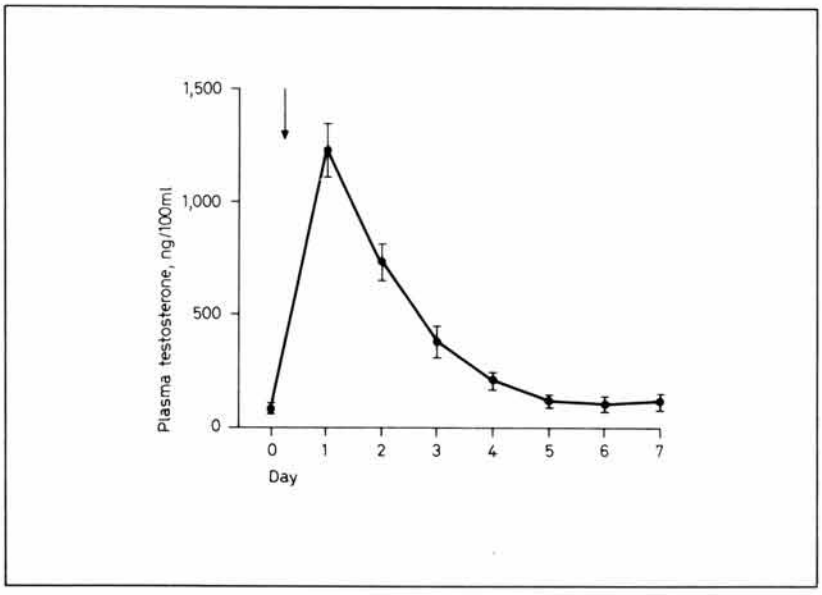

Fig. 3. Effect of 50 mg testosterone propionate on plasma testosterone in seven men with pituitary insufficiency.

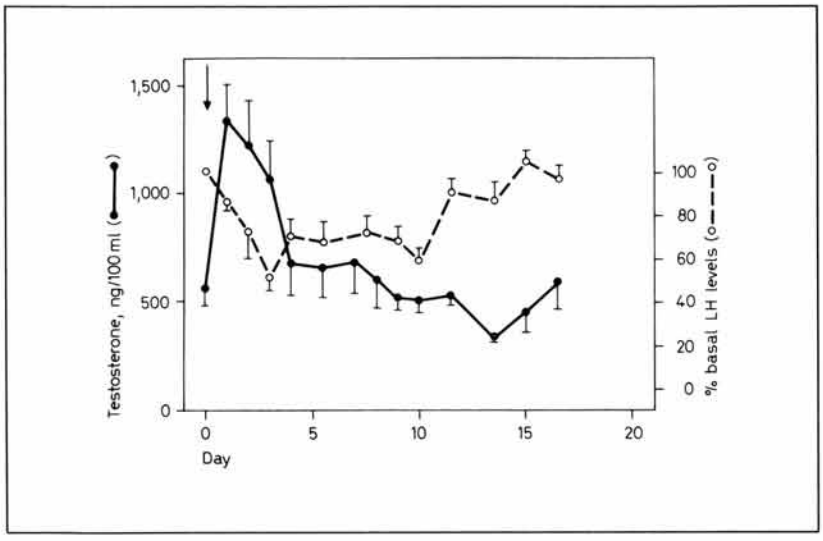

Fig. 4. Effect of 250 mg testosterone oenanthate on plasma testosterone and LH levels in four normal men.

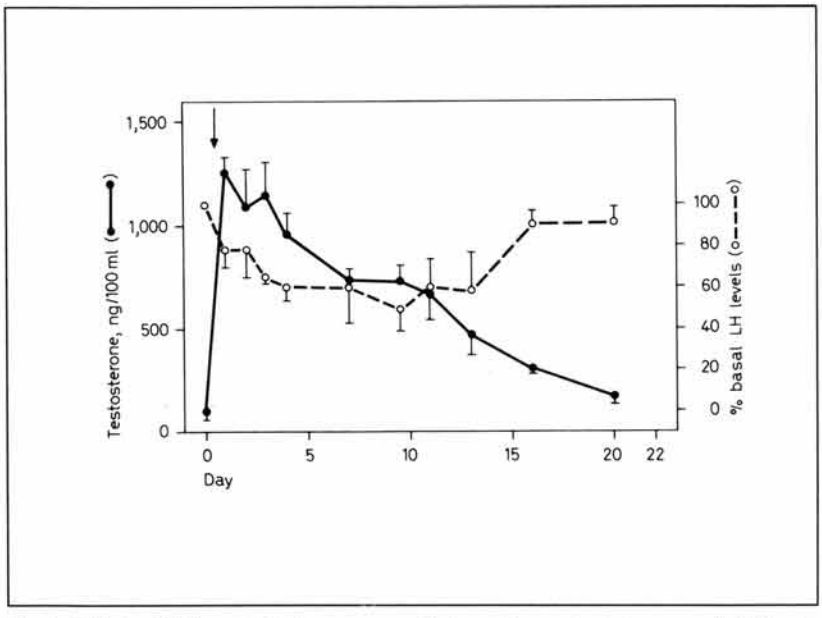

Fig. 5. Effect of 250 mg testosterone oenanthate on plasma testosterone and LH levels in seven men with primary hypogonadism.

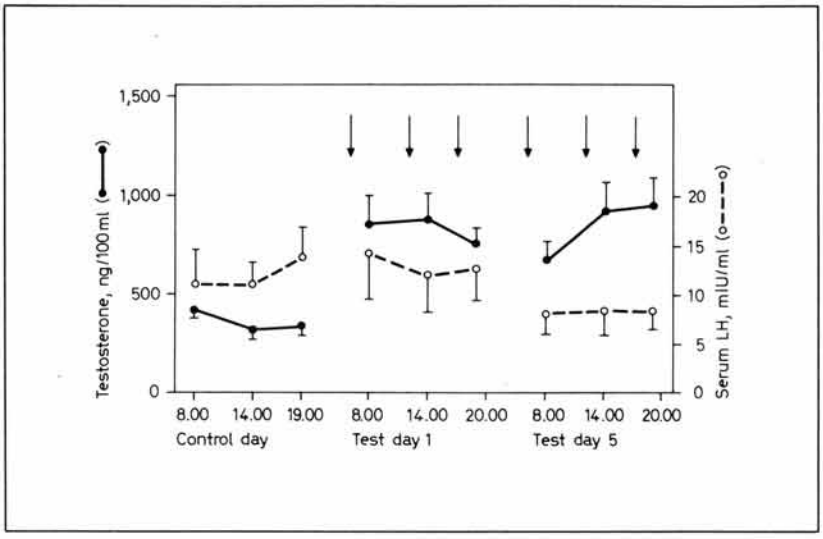

Fig. 6. Effect of testosterone suppositories (3 × 20 mg daily) on plasma testosterone and LH levels in six men.

patients with pituitary insufficiency are not shown in figure 3, since all measurements were in the lower sensitivity range of the method.

In subjects receiving testosterone suppositories, elevated testosterone levels of up to 1,000 ng% were seen on the 1st and 5th test days. LH levels were significantly suppressed on the 5th day ($p < 0.01$).

Discussion

The testosterone-metabolizing capacity of the liver and the metabolic clearance rate of testosterone is higher in normal men than in hypogonadal subjects (*Vermeulen,* 1968). We would therefore expect to find a difference in the length of action of the testosterone preparations between these groups. However, no such difference could be demonstrated in this study. Thus we may conclude that the rate of release from the site of injection, rather than the rate of metabolism, is an important factor in determining the duration of effectiveness of a given testosterone ester. In this respect the recent findings of *Bellman et al.* (1976) are of interest as they demonstrate different rates of enzymatic hydrolysis at the site of injection for different testosterone esters.

For long-term therapy of hypogonadism, a long-acting preparation such as testosterone oenanthate is the treatment of choice. In order to achieve levels

consistently above the lower normal range, it appears necessary to apply a dose of 250 mg in biweekly intervals. At present longer intervals are generally recommended (e.g., *Labhart,* 1971; *Wood,* 1975). One phenomenon common to all injectable preparations investigated is the observation of unphysiologically high plasma testosterone levels shortly after administration. Thus it is difficult to maintain balanced plasma testosterone levels with this form of medication. More constant plasma levels may possibly be achieved using testosterone-containing silastic capsules (*Frick,* 1973). These, however, are not available commercially.

Although the physiological importance of the now well-established diurnal rhythm of plasma testosterone (*Nieschlag,* 1974) is not known, it would not be possible to mimic this rhythm with the injectable preparations investigated here (if one should consider this to be of advantage to the patient). In this regard short-acting preparations, such as the testosterone suppositories investigated in this study, or testosterone undecanoate, effective orally (*Nieschlag et al.,* 1975), may allow for a more flexible regimen.

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