Effect of an aqueous suspension of testosterone on men's gonadotropins serum levels and on their changes after GnRH

by

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Previous work from this laboratory ([1]) demonstrated that testosterone propionate given to normal men was able to induce a decrease of the serum levels of gonadotropins.

In the same subjects, the effect of a synthetic gonadotropins releasing hormone (GnRH) injected intravenously under testosterone propinate treatment was not different from the effect of the same dose of GnRH given before testosterone treatment.

Testosterone propionate seemed therefore to promote a negative feed back mechanism, active in gonadotropins secretion regulation, similar to the one observed by Lee *et al.* ([2]) when testosterone was administered in acqueous suspension.

According to those earlier results, it was concluded that testosterone propionate was effective in reducing gonadotropins secretion and that no inhibitory or facilitating effect on the stimulation of gonadotropins release by GnRH was induced in the presence of high testosterone serum levels obtained by testosterone propionate administration.

The testicular hormone seemed therefore to behave differently in man than an ovarian steriod does in woman, where high levels of estradiol are known to induce a greater GnRH stimulated gonadotropins release from the pituitary, as Knobil *et al.* have reported ([3]).

It could be argued, however, that the results obtained in those experiments might depend on the fact that testosterone was administered as its propionic esther and that the experimental set up did not reproduce the one envisaged by Lee *et al.*

The experiment was then repeated using testosterone suspended in water, at the average effective dose proposed by the latter Authors.

MATERIALS AND METHODS

Three healthy men, aged respectively 22, 23 and 48 were given parenterally at 8 a.m. for three days 12.5 mg/day of testosterone in aqueous suspension (Oreton(R), Schering).

LH, FSH and testosterone were determined daily in duplicate on serum samples obtained around 8 a.m. and 4 p.m.

In one case the determination was made also at midnight.

The day before steroid administration and on the third day of treatment LH and FSH as well as testosterone were determined in duplicate twice before

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intravenous rapid administration of 100 μg of a GnRH obtained from Serono Immunochemicals, Rome.

After GnRH administration, serum gonadotropins were monitored as previously described by De Cecco *et al.* ([4]).

RESULTS

The behaviour of testosterone and gonadotropins during the observation period is depicted in figure I.

The plot shows that testosterone and gonadotropins were in all instances within normal range at the beginning of the study.

In these conditions, GnRH induces a prompt rise of both gonadotropins.

Upon testosterone treatment, serum levels of this steroid rise and simultaneously serum LH and FSH fall gradually, reaching a nadir between the second and the third day of testosterone treatment.

In some instances, tropins levels fall below the sensitivity range of the method.

The response to GnRH administered together with testosterone treatment does not differ appreciably from the one observed before treatment onset.

DISCUSSION

The data obtained reproduce the inhibitory effect of testosterone obtained by Lee *et al.*, that were besides consistent with the previous finding by ourselves, obtained using testosterone propionate.

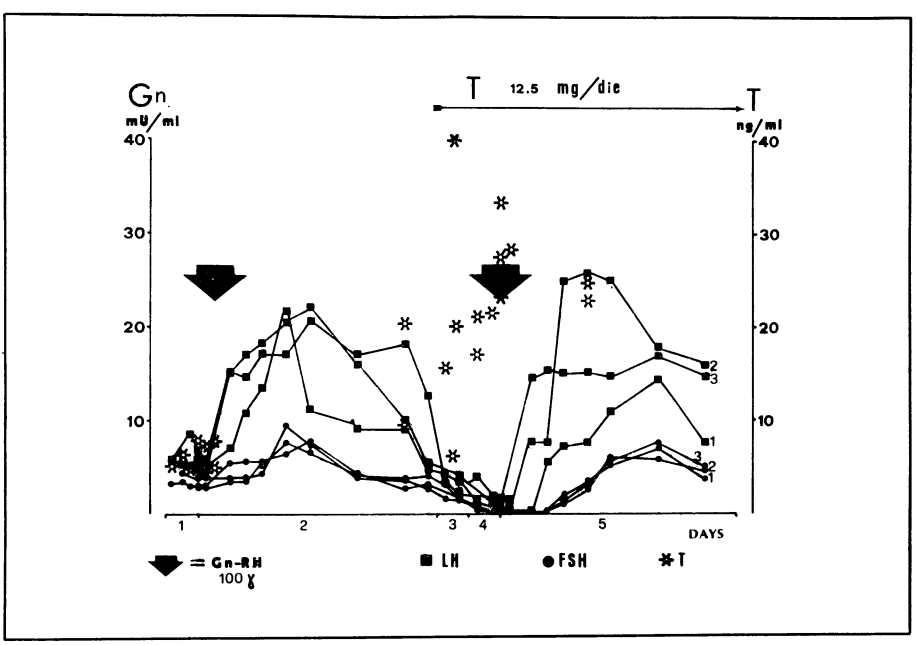

FIG. 1 - Behaviour of LH, FSH and testosterone in serum under the effect of GnRH, testosterone in aqueous suspension and testosterone in aqueous suspension plus GnRH in three normal men. Each point is the average of determinations in duplicate.

Testosterone in aqueous suspension induces a decrease in gonadotropins levels in serum comparable to those obtained by us using testosterone proprionate, but testosterone levels reached with the administration of testosterone in aqueous suspension were comparatively higher than those observed when the propionic esther was used, in spite of the fact that the amount of steroid given was greater in the latter case.

The difference can be ascribed to the different farmaceutical form employed.

It must be stated that a pharmacological evaluation was not the purpose of this work.

The experiment was rather designed to verify whether testosterone, administered in an aqueous suspension, acted similarly to testosterone propionate also in regard to gonadotropins release after pituitary stimulation by GnRH.

The data obtained indicate that testosterone both as the pure steroid and as its propionic esther does not influence pituitary response to GnRH, either in blunting or in facilitating it.

Under this respect the lack of a positive feed-back mechanism operating in the relationship testosterone vs. gonadotropin release is confirmed, at least for the testosterone serum levels considered ([5]).

Using testosterone senantate, von zur Mühlen and Köbberling observed both depressed gonadotropins and unaffected response to GnRH as we did in previous research with testosterone propionate and in the present experiment, though direct comparison with our results is not complete, since the serum levels have not been reported.

In other experiments, the same Authors observed a depression of the response to GnRH, when testosterone plasma levels were kept elevated for weeks and suggest that this was the reason of the effect, rather than the actual concentration of testosterone in plasma.

SUMMARY

Upon testosterone administration in aqueous suspension an inhibition of gonadotropins secretion has been observed.

Pituitary response to GnRH is however unimpaired.

The results are consistent with the previously observed data obtained when testosterone propinate was administered.

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