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Androgen Substitution with Testosterone Containing Nasal Drops

By

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Testosterone proprionate in form of eye drops will not be absorbed. A good absorbtion takes place following the administration of testosterone containing nasal drops in the form of an emulsion of pure testosterone. A quick, significant testosterone increase but of only short duration takes place. Unpleasant side effects were not observed. This treatment may be clinically applicable to male patients in the climacteric period.

Key words: testosterone – nasal drops – endocrine profiles – climacterium virile.

In testosterone deficiency syndromes there are already various possibilities for testosterone substitution which may not necessarily fulfill all requirements of such a method in each case. The oral administration of naturally occuring steroids showed over years a very poor effect because they are almost exclusively absorbed via the portal vein system as has been demonstrated for instance for testosterone in the dog (Martin et al. 1965). They instantly are metabolized and conjugated in the liver and lose their biological activity. Since esterification of testosterone to the apolar testosterone undecanoate results in a considerable increase of oral biological activity this mode of application represents a more favorable way for testosterone substitution (Coert et al. 1975; Franchi et al. 1978; Franchimont et al. 1978; Hirschhäuser et al. 1975; Horst et al. 1976; S. G. Johnson et al. 1974; Nieschlag et al. 1975). Two other possibilities for this purpose are injections (Nieschlag et al. 1976; Frick et al. 1977) and sub-

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cutanecus implantations (Frick et al. 1979) which might have beside some advantages such as administration regimen some disadvantages.

Since more than one method for testosterone substitution is already available, the type of administration may depend on different factors such as the nature of the disease, the length of the substitution period, the basal plasma testosterone levels, the time the effect begins to take place, its duration etc.

In addition to the already existing methods for testosterone substitution we have tried in a pilot study a new route of testosterone application in order to evaluate primarily the endocrine profiles.

Materials and Methods

In the case of 3 patients from 21 to 61 years of age, testosterone propionate was administered in the form of eye drops, specially, in a single dose of 2,5 mg. Plasma testosterone levels were determined from time zero (just before eye drops were applicated) up to 480 minutes after administration in regular intervals.

To a group of 9 patients from 15 to 69 years of age testosterone was administred in the form of nasal drops composed of the following ingredients: 10 mg of testosterone, 5 mg of Methocel (methyl cellulose) to 1 ml of destilled water.* Before and 10, 20, 30, 60, 120, 180, 240, 360, 420 and 480 minutes after the administration of the nasal drops plasma testosterone was measured with a radioimmunological method (Bartke et al. 1973).

Four of nine patients mentioned, from 15 to 56 years old, were administered 5 mg of testosterone (the equivalent of 10 nasal drops) in one dose.

In the case of three patients between 18 and 69 years of age, in addition to the plasma testosterone, the serum gonadotropin and prolactin plasma levels were also measured (Crosignani et al. 1970, Ohgo et al. 1976).

Two patients, 54 and 67 years old, respectively, were given 2,5 mg of testosterone (the equivalent of 5 nasal drops), 4 times altogether, in an interval of 4 h, and plasma testosterone (T) levels were measured 10, 20, 30, 60, 120 and 180 minutes, respectively, after the administration of the nasal drops.

Results

On Fig. 1 one observes that the testosterone proprionate in aqueous solution in the form of eye drops is virtually not absorbed. On the other hand in the case

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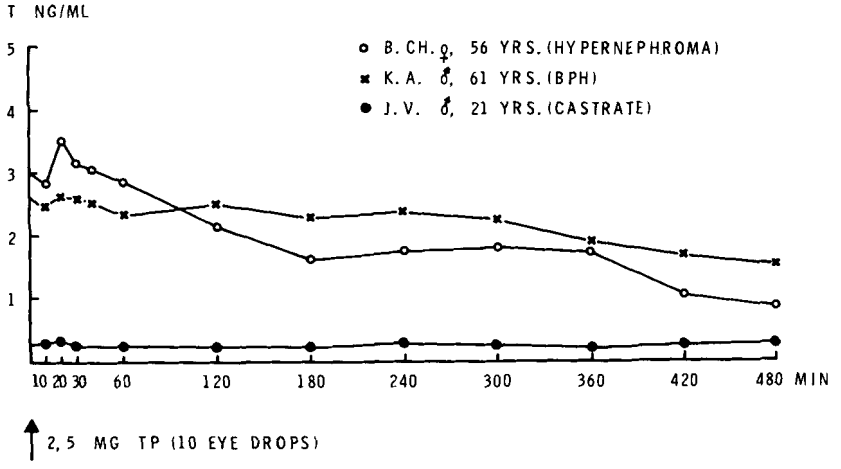

Fig. 1.
Endocrine profiles for plasma testosterone after application of 2,5 mg testosterone proprionate (TP) in form of eye drops.

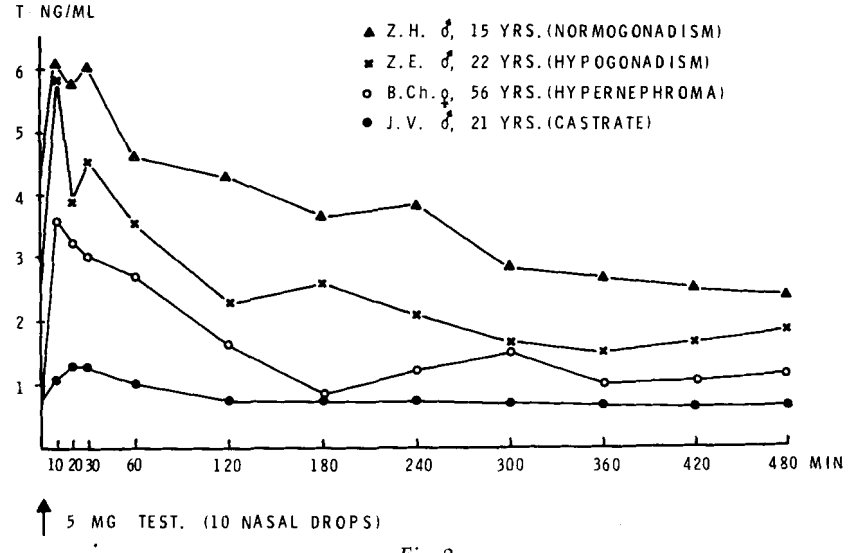

Fig. 2.
Plasma testosterone levels in four subjects after application of testosterone containing nasal drops.

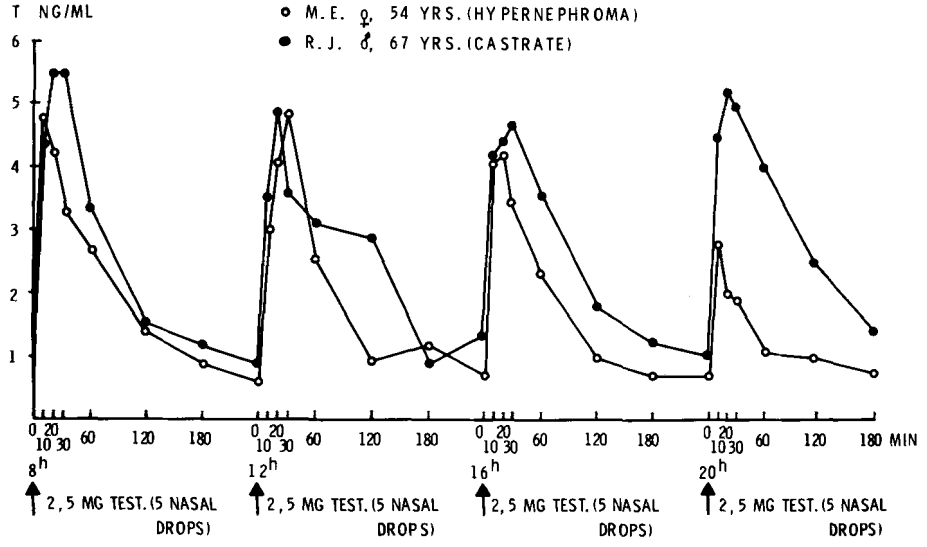

Fig. 3.

Endocrine profiles for plasma testosterone. In each case a single dose of 2,5 mg testosterone was administered through the basal route 4 times in intervals of 4 h.

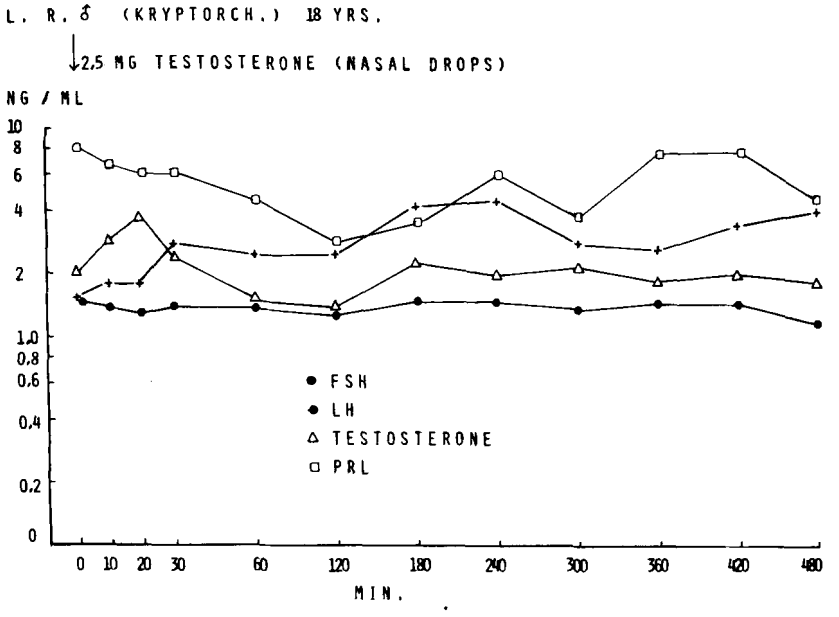

Fig. 4.

Plasma levels for FSH, LH, testosterone and prolactin after application of 2,5 mg testosterone in nasal drops.

of testosterone nasal drops prepared in the form of an emulsion of pure testosterone in spite of the different initial testosterone levels, a very rapid and significant increase of the plasma testosterone takes place, which is however of short duration (Fig. 2). Also with repeated doses at brief intervals, a constantly uniform, pronounced testosterone increase is shown. A cumulative effect does not take place (Fig. 3).

Plasma LH and FSH were determined in 2 cases in addition to testosterone (Fig. 4). Testosterone shows the rapid short lasting increase as already described before. In the plasma LH after 120 minutes – where the plasma – T levels are again in the pretreatment range – a distinct plateau like peak is shown which lasts for another 120 minutes. Plasma FSH shows no significant change throughout the observation period from time zero up to 480 minutes after T-containing nasal drops were given. Plasma prolactin levels (normal range in our laboratory 5–20 ng/ml) fluctuate between the normal daily range.

Discussion

The attempt to administer testosterone in the form of eye drops shows for the present time that testosterone proprionate will not be absorbed as eye drops in aqueous solution. This can be attributed on the one hand to the size of the molecules and on the other hand to the fact that pure substances are better absorbed through mucous membranes than the corresponding esters.

A different situation is present when T-containing nasal drops in a special galenic preparation are administered.

The very rapid and significant testosterone increase, which reaches its maximal level just after 20 minutess, is impressive. An effective level, however, lasts only from 120 to a maximum of 180 minutes.

After four h, an effective testosterone level above the initial level is no longer present. The LH curve seems to indicate that, in the first instance, caused by the rapid and pronounced increase in testosterone, a transient inhibition of the LH secretion takes place with a subsequent excessive reaction of the pituitary gland. The different prolactin levels fall within the limits of the usual daily fluctuations.

As can be seen from these preliminary results after administration of testosterone containing nasal drops in the present galenic preparation there is a rapid and significant increase in plasma testosterone levels which are comparable with those found in subjects treated with 40 mg testosterone undecanoate per day orally (Franchi et al. 1978). But the duration of probably sufficient elevated testosterone plasma levels might be too short for an effective testosterone substitution with this mode of application.

In this regard further studies with a different galenic preparation which might maintain longer lasting elevated plasma testosterone levels have to be done. The mode of application through the nasal route could be an advantage in many instances to bypass the intestinal tract and to overcome the intestinal inadequacies which occur from time to time and which cause an altered absorption.

The resorption of testosterone through the nasal mucosa is very rapid as demonstrated by the endocrine profiles. Also a regular administration in a 4 hrs. interval shows no accumulative effect but with this mode of application plasma testosterone levels are reached which are at least 100 % higher as the initial pretreatment values (Fig. 3).

To draw already final conclusions about the practicability of such a testosterone substitution method would be to early and hypothetic until further investigations are done in regard of the practicability, of the possibility to maintain longer lasting constant plasma testosterone levels and of the occurence of possible undue side effects.

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