

Nasal application of testosterone (Nasobol®)

Serum testosterone concentration after Nasobol® administration compared to the daily fluctuations in the profile of healthy men

Remarks on chronobiology of hormone release

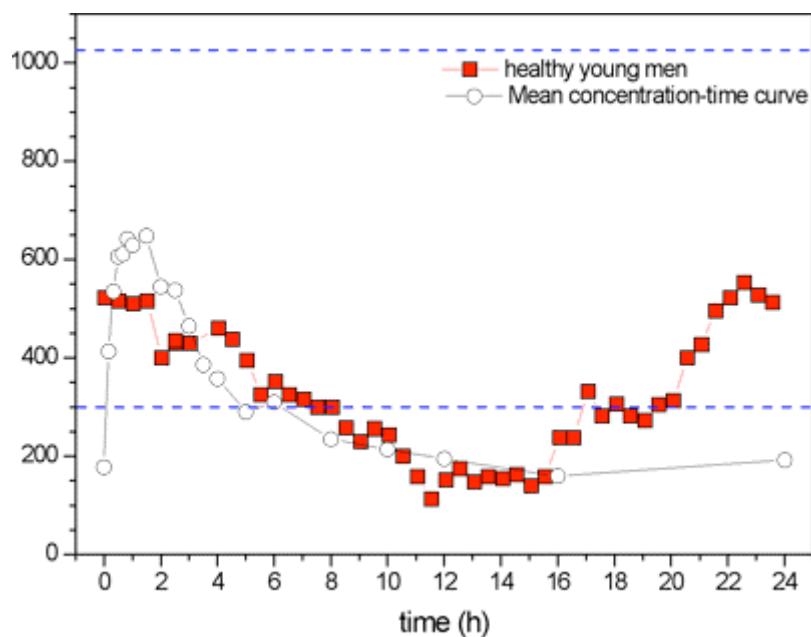
Various means of supplementation of low testosterone levels have been tried over the years. Often with only a moderate degree of success, due mainly to low bioavailability and the ability to achieve and maintain normal physiological fluctuations in the concentration of circulating testosterone (definition Consensus Conference on Androgen Therapy: „...the major goal of therapy is to replace testosterone levels at as close to physiologic concentrations as is possible...“).

An essential point of the debate is to come to terms with what is a physiological hormone replacement therapy. At the moment it is assumed that HRT in men involves nearly constant testosterone levels over 24 h.

In contrast are the published data by Diver (1, 2), Spratt (3) and Walton et al (4) (among others). Between 16:00 h and midnight the testosterone concentration of a healthy man is at its lowest, and no doubt can clearly fall below the lower limit of the reference range for the testosterone morning concentration (300 ng/dl). This means that in healthy men the hormone concentrations are not a circadian continuum but fluctuate considerably. In the early morning hours testosterone concentration shows a large increase reaching a peak between 7-8 h and then shows a relative plateau until 10:00 h approximately.

In his publication from 2003 for example Diver shows a marked diurnal variation in serum total testosterone, with a minimum decrease of 43% of the peak value. Although all subjects had a peak level > 10 nmol/l, 50% of the subjects reached a nadir of < 10 nmol/l. Thus it can be observed that the normal physiological secretions of the endocrine system describe a variable pattern of production with little evidence that constant secretion is the preferred option.

A novel preparation of testosterone replacement in the form of a nasal gel (Nasobol®), administered simultaneously to each nostril, has recently been subjected to clinical trials (phase II) in hypogonadal men (see graph 1, time 0 is 08:00 h).



Graph 1: Mean concentration-time-curve after intranasal application of Nasobol® (7.6 mg testosterone once, black line) in comparison to testosterone profile of a healthy young man (red line, data taken from Diver 2006 [table 1])

The concentration-time curve of testosterone following dosing with Nasobol® in principle imitates the course determined in healthy men. The diagram points out the similarity of the profiles. How perfectly the curves harmonize depends not least on the initial condition of the patient.

It can be concluded that the daily single application of Nasobol® is much closer (i.e. more physiological) to the natural day-profile of testosterone than any other application form available at the moment.

Nasal applications lacks many of the different disadvantages of other products such as skin-to-skin transfer, stickiness, unpleasant smell (gels), skin irritation (patches), elevated DHT (patches and oral), injection pain and high T and DHT peaks (intramuscular injection), food interaction (oral). Instead, nasal application is simple and easy to use. Testosterone levels after nasal application follow the normal diurnal pattern of serum testosterone for the greater part of the day whereas virtually all other products give more or less "constant" steady state levels.

1 Diver MJ, Imtiaz KE, Ahmad AM et al

Diurnal rhythms of serum total, free and bioavailable testosterone and of SHBG in middle-aged men compared with those in young men
Clin Endocrinol; 58; 710-717 (2003)

2 Diver MJ

Analytical and physiological factors affecting the interpretation of serum testosterone concentration in men
Ann Clin Biochem; 43: 3-12 (2006)

3 Spratt, DI, O'Dea LSTL, Schoenfeld, D, Butler J, Rao PN, Crowley WF jr.

Neuroendocrine-gonadal axis in men: frequent sampling of LH, FSH, and testosterone
Am.J.Physiol. 254 (Endocrinol.Metab.17): E658-E666 (1988)

4 Walton MJ et al

A diurnal variation in testicular hormone production is maintained following gonadotrophin suppression in normal men
Clinical Endocrinology 66, 123-129 (2007)