ORIGINAL RESEARCH—ENDOCRINOLOGY

Vaginal Application of Testosterone: A Study on Pharmacokinetics and the Sexual Response in Healthy Volunteers

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ABSTRACT

Introduction. Androgen substitution is advocated to improve sexual functioning in women with androgen insufficiency. Nevertheless, the role of androgens in female sexual functioning is not yet unraveled. Even less is known about changes in androgens and the female sexual response.

Aim. The aim of the study is to describe the pharmacokinetics of a single dose of vaginally applied testosterone. In addition, the study aims to gain more insight into the relation between acute changes in testosterone levels and the sexual response in women.

Methods. A randomized, double-blind, crossover study design was used to compare a single vaginal dose of testosterone propionate (2 mg) with placebo. Ten healthy premenopausal women participated. Serum levels of testosterone, free testosterone, and estradiol were measured. The sexual response was measured before application of medication and 4 and 8 hours after application. Erotic video fragments and erotic fantasies were used as stimuli. The genital sexual response was measured using vaginal plethysmography. The subjective sexual response was measured using a visual analog scale.

Results. Vaginal administration of testosterone propionate induced a significant rise in serum testosterone levels and free testosterone levels, but not in serum estradiol levels. Peak levels were reached after 5.5 hours (range 2–12 hours). Mean peak levels of testosterone were 7.71 nmol/L after testosterone propionate and 2.99 nmol/L after placebo ($P < 0.005$). Mean peak levels of free testosterone were 0.12 nmol/L after testosterone propionate and 0.04 nmol/L after placebo ($P < 0.005$). Despite marked elevated levels of androgens this study was unable to detect a direct effect on the genital or subjective sexual response.

Conclusions. A single dose of vaginally applied testosterone propionate elevates serum levels of testosterone and free testosterone within 6 hours. Nevertheless, this acute rise in androgens has no effects on the female sexual response. **Apperloo M, Midden M, van der Stege J, Wouda J, Hoek A, and Weijmar Schultz W. Vaginal application of testosterone: A study on pharmacokinetics and the sexual response in healthy volunteers. J Sex Med 2006;3:541–549.**

Key Words. Vaginal Application; Testosterone Propionate; Pharmacokinetics; Sexual Response; Vaginal Plethysmography

Introduction

Low androgen levels in women may lead to symptoms including sexual dysfunction, in particular decreased libido, loss of sexual responsiveness, or decreased sexual arousal [1]. A specific level of testosterone in women that can be considered diagnostic for androgen deficiency has not been established. The Princeton consensus meeting 2001 advocates estrogen substitution to relieve the symptoms and to improve sexual functioning in these cases [1]. Nevertheless, although

different aspects of female sexual functioning are enhanced due to androgen substitution [2–6], presently there are very few data to suggest that this treatment actually improves sexual satisfaction [7].

The role of androgens in female sexual functioning has not yet been unraveled. Brain imaging during sexual arousal shows specific areas involved in sexual responding [8]. Androgen and estrogen receptors are present in the brain but it is not yet clear whether androgens can directly affect the brain, or indeed whether effects occur after aromatization of androgens into estrogens [9]. The effects of testosterone in target organs can originate via binding to intracellular androgen receptors, via transformation of androgens into dihydrotestosterone by means of 5 alpha-reductase, and finally via transformation into estrogens by means of aromatase. Androgens can also have nongenomic effects, often involving ion fluxes through interactions with the cell membrane [10].

The female sexual response is a complex process involving body and mind. A certain mental state is required in which women are willing to be receptive to sexual stimuli and to allow sexual arousal, both subjective excitement and the physical response [11].

The genital sexual response involves the sympathetic and parasympathetic nerves and is characterized by relaxation of the vaginal vascular and nonvascular smooth muscle cells. Hereby the pressure in the capillary bed is increased and causes vaginal vasocongestion and transudate to moisten the vaginal wall [12]. The exact mechanism of genital arousal is not yet understood. Animal studies suggest a role for neurotransmitters, like nitric oxide, acetylcholine, and vasoactive intestinal polypeptide, and for hormones like estrogens and androgens in the local regulation of vaginal smooth muscle cells [13,14]. Several preparations of androgens are used in studies on treatment of androgen insufficiency in women but none of them have been approved by the Food and Drug Administration for androgen insufficiency syndrome [15]. There is growing interest in the vaginal route of administration of drugs, especially steroid hormones. In a recent review the advantages of vaginal application were summarized. In vaginal application the hepatic first-pass effect is avoided allowing lower dosing. This can result in lower systemic exposure plus lower incidence of side-effects. Absorption is unaffected by gastrointestinal disturbances. Vaginal application is both easy and painless, in addition to allowing self-administration [16]. Vaginal estrogen preparations are effective, as well as generally safe for ameliorating urogenital atrophy. Furthermore, the preparation can improve vaginal lubrication and reduce dyspareunie [17,18]. To our knowledge there are no known studies that have investigated the subject of vaginal administration of androgens.

Moreover, there are very few studies investigating the acute effects of androgen substitution on female genital and subjective arousal. Tuiten et al. found an increase in the genital sexual response in women after administration of a single sublingual dose of testosterone [19]. Additionally, they found a strong association between the increase in genital responsiveness and subjective feelings of genital sensations and sexual desire. Meston and Heiman studied the effects of a single oral administration of dehydroepiandrosterone (DHEA) in women [20]. Although DHEA significantly increased blood levels of DHEA sulfate, no effects on either physiological or subjective measures of sexual arousal were noted.

We were interested in the pharmacokinetics of vaginally applied testosterone and the relation between rapid changes in androgen levels and the female sexual response. To gain more insight in this matter we performed a randomized, double-blind, crossover study comparing a single dose of vaginally applied testosterone propionate with placebo in healthy volunteers.

Methods

Subjects

Ten healthy, sexually functional women were recruited through advertisements. Their median age was 23 years (range 20–41 years). All participants were premenopausal with regular menstrual cycles. They were all nonobese. None of them had been using hormones, including oral contraceptives, during the last 3 months. During the study days participants were asked not to use drugs or alcohol and to refrain from sexual activities. Participants were informed about both the procedure and the aim of the study and agreed to sign an informed consent form, which they duly did. Confidentiality was assured and the subjects could withdraw from the study at any time.

Design

The study consisted of two experimental days during which testosterone or placebo was administered. As previously stated, a randomized, double-blind, crossover design was used. The