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Intravaginal prasterone (DHEA) provides local action without clinically significant changes in serum concentrations of estrogens or androgens

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ABSTRACT

In order to avoid the risks of non-physiological systemic exposure, serum concentrations of estradiol (E_2) and testosterone (as measured by mass spectrometry-based assays) should remain below the 95th centiles measured at 9.3 pg/ml and 0.26 ng/ml for these respective sex steroids in normal postmenopausal women. To document the possibility of achieving this therapeutic objective, we have measured individual 24 h serum E_2 and testosterone concentrations in women with vulvovaginal atrophy (VVA) receiving daily intravaginal administration of a clinically effective dose of 6.5 mg prasterone (dehydroepiandrosterone, DHEA).

Serum E_2 and testosterone, as well as DHEA and nine of its other metabolites, were assayed at ten time intervals over 24 h on the first and seventh days of daily vaginal administration of 6.5 mg prasterone.

No significant change from baseline of average 24 h serum E_2 or testosterone concentrations was observed. Moreover, average 24 h serum DHEA remained within the normal postmenopausal range. Estrone sulfate and the androgen metabolites androsterone glucuronide and androstane-3α, 17β-diol glucuronide did not change, thus confirming the absence of any biologically relevant systemic exposure to estrogens and androgens, respectively.

Serum concentrations of metabolites of both estrogens and androgens remain within the normal postmenopausal range following daily intravaginal administration of 6.5 mg prasterone. As other studies have shown, local formation of sex steroids in peripheral tissues without significant release of E_2 or testosterone in the circulation can be achieved with intravaginal prasterone. Thus, prasterone is a promising physiological and attractive solution to treating VVA symptoms.

1. Introduction

At time of menopause, under physiological conditions, secretion of estrogens in the circulation ceases [1]. Vulvovaginal atrophy (VVA) is a common and persistent condition with high prevalence, as approximately half of all postmenopausal women will experience symptoms related to urogenital atrophy [2,3].

Despite its established prevalence, only about 25% of symptomatic women seek medical help, partially due to reluctance to discuss intimate and private issues related to vaginal health [3]. Other than over-the-counter lubricants and moisturizers having limited efficacy, current treatment for VVA is limited to estrogen therapy [4]. Moisturizers and lubricants can provide temporary symptomatic relief (coital comfort), but they do not treat the underlying cause of the condition [5]. In addition, the majority of women with VVA are not treated and/or are looking for an alternative treatment to estrogen-based therapy.

The challenge for an effective and well tolerated treatment of the vaginal symptoms related to sex steroid deficiency following menopause is to avoid systemic exposure to estradiol (E_2) and testosterone. An attractive approach to achieve this goal is through dehydroepiandrosterone (DHEA). Dehydroepiandrosterone, DHEA, an endogenous inactive compound by itself, is converted to estrogens and/or androgens in peripheral tissues which possess the required steroidogenic enzymes [1,6,7] into cell-specific intracellular E_2 and testosterone by the mechanisms of intracrinology [8–10].

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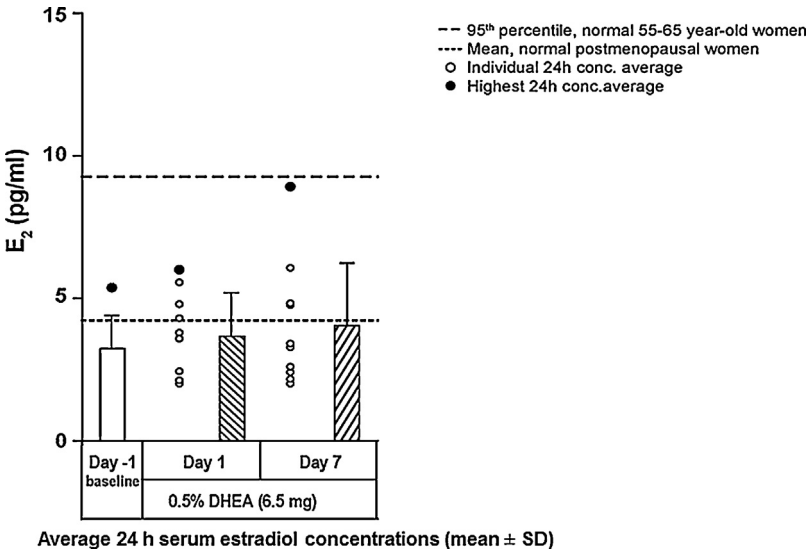

Fig. 1. Average 24 h serum estradiol concentrations. This figure displays the average individual or mean of individual average 24 h serum estradiol (E_2) levels at baseline and days 1 and 7 in postmenopausal women who received daily intravaginal administration of 0.5% (6.5 mg) prasterone ovules.

DHEA, especially in the brain, has been suggested to act through a series of neuronal signaling pathways [11].

Prasterone (DHEA), administered locally in the vagina, is a non-estrogen precursor that enters vaginal cells and gets converted intracellularly to both estrogens and/or androgens depending upon the cell type, thus exerting rapid beneficial effects on VVA [12] as well as on sexual dysfunction [13]. Outside the vaginal cell, there is no meaningful increase in estrogen (serum E_2) or androgen (serum testosterone) concentrations [8–10].

Here, we detail the results of 24-h individual serum concentrations of E_2, testosterone plus DHEA and nine other metabolites (from [9,10]) after the first and seventh daily administration of 0.5% (6.5 mg) intravaginal prasterone, the maximal dose used in current Phase III clinical trials for VVA.

2. Subjects and methods

2.1. Subjects

Forty postmenopausal women with one or more self-identified symptoms of VVA (criteria detailed in [9,10]) were included in this study. The mean age of the women who received the daily

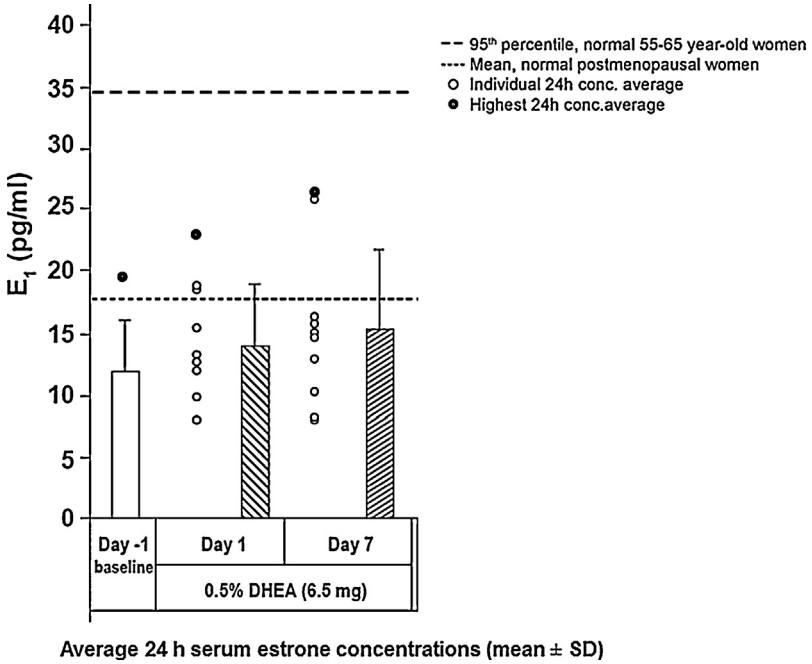

Fig. 2. Average 24 h serum estrone concentrations. This figure displays the average individual or mean of individual average 24 h serum estrone (E_1) levels at baseline and days 1 and 7 in postmenopausal women who received daily intravaginal administration of 0.5% (6.5 mg) prasterone ovules.