Pulsatile administration of testosterone by the vaginal route using Pentravan®

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SUMMARY

Testosterone deficiency occurs during menopause and may be associated with the appearance of a variety of symptoms in addition to its negative effect on sexuality. In the present study, testosterone was administered in the vulval/vaginal region at a dose of 3 mg/ml dissolved in a Pentravan® emulsion (Fagron, the Netherlands) to patients with symptoms of androgen deficiency and testosterone levels in the lower normal range. Vulval/vaginal application of testosterone in Pentravan® increased blood levels of testosterone in a pulsatile manner from 20 ± 15 ng/dl (mean ± SD) (n=26) to 312 ± 264 ng/dl (n=13) after 3 hours, followed by a rapid fall to 67 ± 40 ng/dl and 26 ± 10 ng/dl 12 and 24 hours, respectively, after application. An improvement in sexuality and the sensation of well being was reported by 88% of the patients, with very few side effects. There was also a positive effect on vaginal atrophy.

INTRODUCTION

Testosterone plays an important role in women's health during menopause, not only because it interacts with the androgen receptor, but also due to its transformation into estrogen through the action of aromatase whose expression in the tissues increases with age (1). Estrogen synthesis in the tissues is pivotal for achieving optimal hormonal balance during menopause, since it occurs in all tissues except in the normal breast and endometrium. This process, however, is affected by the blood levels of sex hormone binding globulin (SHBG), by total testosterone level and ultimately by the amount of aromatase activity in the tissue (1). Presently, only total testosterone production, which diminishes with ageing, and SHBG levels can be manipulated in women in order to boost tissue estrogen production. Although there

is a compensatory increase in aromatase tissue activity in women after 50 years of age in response to rising interleukin-6 levels, this may not suffice to compensate for the declining production of testosterone or its precursors, thus resulting in the onset of symptoms of both androgen and estrogen deprivation (2). In addition to being an essential precursor to estrogen synthesis, testosterone is also endowed with a potent antiinflammatory effect through the blockade of the NF-Kappa.b activation pathway (3). During ageing, there is an increase in both subclinical chronic inflammation and NF-Kappa.b activation, which may be the underlying cause of several diseases that affect elderly people such as atherosclerosis, Alzheimer's disease, osteoporosis, sarcopenia and depression as well as an increased risk of cancer (4-7). The mechanisms responsible for the increase in NF-Kappa.b activation with ageing are largely unknown; however, it may be one of the consequences of the reduction in testosterone production, since this steroid hormone is capable of suppressing NF-Kappa.b activation and its subsequent translocation to cell nuclei where it would stimulate the transcription of inflammatory genes. In fact, the administration of testosterone to postmenopausal women is able to reduce the production of inflammatory markers such as tumor necrosis factor alpha (TNFα) by macrophages. It is currently being proposed that it may be possible to ameliorate some of the symptoms or medical conditions associated with ageing in women by replacing testosterone. The present study is a preliminary report on the vulval-vaginal absorption of testosterone when used in a new emulsion, Pentravan®.

MATERIAL AND METHODS

Menopausal patients with symptoms related to androgen deficiency such as fatigue, lack of libido and mild depression were included in this preliminary study to investigate testosterone absorption when used in a Pentravan® emulsion. Testosterone was administered to the vulval region, between the labia minora, at a dose of 3 mg/ml, dissolved in a Pentravan® emulsion (Fagron, the Netherlands), to patients with symptoms of androgen deficiency and testosterone levels in the lower normal range. Blood was drawn 3, 12 and 24 hours after testosterone administration to measure absorption. The impact of this treatment on sexuality and quality of life was evaluated.

RESULTS

Administration of testosterone in a Pentravan® emulsion to the vulval/vaginal region of postmenopausal women increased blood levels of testosterone from 20 ± 15 ng/dl (mean ± SD) (n=26) to 312 ± 264 (n=13) after 3 hours. This increase was followed by a rapid fall to 67 ± 40 ng/dl and 26 ± 10 ng/dl (n=13) 12 and 24 hours, respectively, after application. Unlike testosterone, no change was found in SHBG levels during this period. An improvement in sexuality and the sensation

of well being was reported by 88% of the patients (23/26). Estradiol blood levels were low prior to testosterone administration and remained stable during the vaginal administration of this hormone. No adverse events were observed. An increase in the percentage of superficial cells was found in the vaginal smears 4-6 weeks after initiation of the vaginal administration of testosterone.

CONCLUSION

The application of testosterone in a Pentravan® emulsion to the vulval/vaginal region of postmenopausal women caused a rapid rise in blood levels of this hormone, which returned to baseline levels after 12 hours. An improvement in the symptoms of androgen deficiency was reported by the majority of patients, with very few side-effects. This may prove to be a practical and effective way of administering testosterone to postmenopausal women with signs and symptoms of androgen deficiency. The use of the vaginal route to replace testosterone may mimic the physiological secretion of this hormone, since in both sexes testosterone secretion is pulsatile rather than continuous (8). The oral route may not be the best mode of administering testosterone, since this hormone is easily degraded during its passage through the gastrointestinal tract, thus greatly limiting its absorption into the circulation (9). Although this was ingeniously resolved by developing testosterone esters that were more resistant to this digestive process, these synthetic androgens may provoke adverse events that are not found with the use of bioidentical testosterone. Exposure of the liver to high levels of synthetic steroids during their first passage may surpass this organ's enzymatic capability to metabolize these compounds, thus resulting in liver damage. For this reason, safe and easy non-oral routes of administering testosterone are necessary in order to permit replacement of this hormone for prolonged periods of time during menopause to treat the medical conditions associated with androgen deficiency (10). In these patients, bioidentical testosterone will not only interact with the androgen receptors, but will also be converted to estradiol in the tissue through the action of aromatase (1). The administration of testosterone by the vaginal route, as reported in the present paper, mimics testosterone pulsatility and theoretically this may avoid excessive receptor stimulation, thus explaining the low incidence of side effects.

This route may prove beneficial for the administration of testosterone to menopausal women with signs of androgen deficiency and testosterone levels in the lower quartile of the normal range. The vulval/vaginal administration of testosterone in a Pentravan® emulsion also provokes a pulse-like increase in testosterone levels during the first three hours of administration, reaching values above the normal range for women. However, the rapid return to baseline levels in less than 12 hours may avoid the sustained stimulation of the androgen receptor, thus explaining the low incidence of androgenic side effects. The conversion of testosterone into estradiol in the tissues thorough the action of aromatase may also limit excessive androgenic

stimulation in these patients besides providing a selective manner through which to replace estrogens during menopause, since under normal circumstances aromatase expression is absent in the breast and endometrium. The increase in the vaginal maturation index following testosterone administration may provide a simple and inexpensive means of evaluating this tissue conversion of testosterone into estradiol.

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