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Case Report

Weekly vaginal administration of tamoxifen for three months in postmenopausal women with vulvar and vaginal atrophy: a possible new treatment approach?

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Summary

An exploratory study was conducted recruiting four healthy postmenopausal women suffering from vulvar and vaginal atrophy (VVA). Subjects self-administered vaginal suppositories containing tamoxifen (20 mg). Subjects were instructed to insert one suppository vaginally once daily for one week and twice weekly over a period of three months. Vaginal pH and dryness scores using a visual analog scale (VAS) were recorded at enrollment and subsequent assessments were recorded using self-assessment questionnaires over a three- month period. Serum tamoxifen levels were measured after two months of suppository use. After three months, both vaginal pH and vaginal dryness symptoms showed significant improvement. Vaginal pH scores improved approximately 30% compared to baseline by completion of the study. Vaginal dryness scores improved approximately 63% compared to baseline. As expected, serum tamoxifen levels were negligible ranging from 1.0 ng/ml to 10.0 ng/ml determined after eight weeks on the treatment. The present results suggest that delivery of tamoxifen directly to the vaginal epithelium for the treatment of VVA may be a viable new treatment approach. Therefore, this route of administration may offer an important treatment modality for patients with a history of breast cancer, at risk for breast cancer, and who have hormone-receptor-positive breast cancer, including estrogen receptor-positive (ER-positive), and progesterone receptor-positive (PR-positive) in addition to node negative breast cancer.

Key words: Vulvar and vaginal atrophy; Tamoxifen; Vaginal pH; Vaginal dryness.

Introduction

Tamoxifen has been widely prescribed for the adjuvant treatment of breast cancer since its approval in 1977 (NDA 17-970) [1]. In 1986, tamoxifen gained FDA approval for therapy in postmenopausal node positive women and has subsequently been proven effective in hormone receptor positive premenopausal and node negative breast cancer patients [2], breast cancer prevention [3] and ductal carcinoma in situ (DCIS) [4]. Tamoxifen remains the only FDA-approved hormone modulating agent for the treatment of breast cancer and DCIS in premenopausal women. Tamoxifen and its metabolites are known as estrogen receptor (ER) antagonists. Tamoxifen is systemically metabolized to 4-hydroxy-tamoxifen and N-desmethyl-tamoxifen followed by conversion to endoxifen. Tamoxifen metabolites have been shown to antagonize ER binding both in *vitro* and in *vivo* [5]. However, the primary therapeutic effect of tamoxifen as an anticancer agent is thought to be derived from its anti-estrogen properties; this agent also has been shown to have modest estrogenic activity [6]. Tamoxifen has been reported to exert an estrogen-like response on vaginal cytology by a mechanism yet to be understood and not expected based upon its an anti-estrogen activity [7]. Tamoxifen as a treatment of vulvar and vaginal atrophy (VVA) in postmenopausal women with breast cancer has been investigated in several clinical trials since its original approval. Twelve clinical trials that included a total of 745 patients treated have reported positive results of tamoxifen on VVA in women receiving tamoxifen for breast cancer [8-19]. All trials showed substantial improvement in vaginal maturation index and/or in vaginal pH as objective endpoints in the treatment of VVA.

VVA is defined as inflammation of the vaginal epithelium due to atrophy secondary to decreased levels of circulating estrogen [20]. Historically, estrogen creams, rings, and tablet supplements have been prescribed for the vaginal symptoms of VVA. However, estrogen therapy is contraindicated in breast cancer patients or patients with a genetic predisposition or history of familial disease because of the concern that its use will promote occult disease.

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Three prospective randomized controlled studies of estrogen treatment in symptomatic early-stage breast cancer survivors had to be stopped prematurely because interim analyses suggested an increase in breast cancer recurrence and metastatic disease [21-23].

The North American Menopause Society (NAMS) current position statement regarding the treatment of symptoms of VVA associated with menopause states that vaginal products should be considered [24]. Therefore, an ideal treatment for VVA in high-risk patients may be the use of vaginally administered tamoxifen. Consequently, this exploratory study was initiated to evaluate the potential safety and efficacy of a vaginal suppository compounded with 20 mg of tamoxifen, which was self-administered daily for one week and then twice weekly for a total of three months. The primary objective of this exploratory study was to evaluate the efficacy of locally self-administered tamoxifen in treating VVA using two key parameters: (1) the self-assessment of vaginal dryness, and (2) normalization of vaginal pH. A secondary objective was to measure serum tamoxifen concentrations to determine the systemic exposure.

Table 1. — *Median pH score and vaginal dryness symptom score, and paired differences between the enrollment and month 3 visits.*

	n	Median*	Range*	$p^{\dagger}$
pH enrollment	4	7.1	6.5 – 7.5	
pH month 3	4	5.0	5.0 – 5.2	
Paired difference	4	-2.0	-2.5 – -1.5	0.07
Vaginal dryness enrollment	4	8.0	7.5 – 9.0	
Vaginal dryness month 3	4	3.0	2.0 – 3.0	
Paired difference	4	-5.5	-6.0 – -4.5	0.07

**A negative value indicates a decrease from enrollment whereas a positive value indicates an increase from enrollment.*

† P-value from Wilcoxon signed rank test which compared the enrollment value to the three-month value for each participant.

Table 2. — *Systemic levels of vaginal tamoxifen after eight weeks of treatment.*

Patient	Serum tamoxifen (ng/ml)
001	10.0
002	9.6
003	1.0
004	2.0
Median	5.8

Case Report

An open-label prospective cohort study with no placebo arm was conducted recruiting four healthy postmenopausal women with VVA. The four subjects evaluated had a mean age of 55.5 years, range 52-63, and mean of 7.7 years post-menopause, range 2-15 years. All subjects were Caucasian. Tamoxifen is an approved drug as such enabled us to perform this exploratory study without an IRB approval. Subjects were consented for treatment. No subjects refused treatment. Subjects underwent one screening visit. Subjects were evaluated by one observer for vaginal pH (vaginal pH Test paper 4.5-7.5 pH) and vaginal dryness based on VAS measurements. Vaginal dryness was rated using a VAS; the scale ranged from 0 (participant was not bothered by the dryness) to 10 (participant was extremely bothered by the dryness). If the subject met the eligibility criteria, including a vaginal pH greater than 5, subjects were then instructed on self-administration and received study medication. The rationale for dosing was based on clinical data demonstrating that tamoxifen 20 mg to 40 mg orally is likely to be beneficial in the treatment of VVA. The rationale for frequency (daily for one week then twice weekly) was based on other FDA approved vaginal products for the treatment of VVA. All subjects received medication as a vaginal suppository composed of tamoxifen [20 mg] formulated by a compounding pharmacist. The pharmacy procedures, quality control, and supply schedule were consistent with compounding regulation guidance. Subjects received a three-month supply of study drug. Subjects were instructed to self-administer the suppository vaginally once per day for one week and then twice per week thereafter. After eight weeks of suppository use, blood levels of tamoxifen were measured. Subjects inserted the suppository and remained supine for one hour prior to serum level determinations assessed five hours later (using high perfomance liquid chromatography/tandem mass spectrometry (LC-MS/MS). At three months, subjects returned for a repeat vaginal pH measurement, and an assessment of vaginal dryness that was conducted as described above.

The primary efficacy endpoints examined were normalization of vaginal pH and improvement of vaginal dryness. Differences in primary endpoints were determined by the self-assessment of vaginal dryness as determined by VAS and for vaginal pH changes by subtracting three-month values from baseline measurements. Descriptive statistics provided for the continuous study endpoints included median and range. Descriptive statistics provided for categorical endpoints included frequency and percent. Wilcoxon Signed Rank test was used to evaluate the median change in vaginal pH and dryness from enrollment to the three-month visit.

Safety assessments consisted of monitoring and recording all adverse events and serious adverse events. Blood levels of tamoxifen were measured after eight weeks of vaginal tamoxifen administration. The blood tests were measured taken five hours after vaginal tamoxifen administration. The secondary endpoint was the measurement of tamoxifen concentrations after eight weeks of vaginal tamoxifen administration.

This exploratory study demonstrated that tamoxifen was effective when delivered intravaginally for three months in postmenopausal women suffering with VVA. The median vaginal pH at enrollment was 7.1 (range 6.5-7.5). At month 3, the median vaginal pH was 5.0 (range 5.0-5.2). The median paired difference between baseline and month 3 was -2.0, with a range of -2.5 to -1.5 ($p = 0.07$, Table 1). The self-assessment of vaginal dryness improved between baseline and month 3. At baseline, the median baseline vaginal dryness rating was 8.0, with a range of 7.5-9.0. At month 3, the median vaginal dryness rating was 3.0, with a range of 2.0-3.0. The median change between baseline and month 3 was -5.5, (range -6.0- –4.5, $p = 0.07$).

All subjects who received vaginal tamoxifen completed their visits for treatment and evaluation. There were no patient dropouts, serious adverse events that occurred during the study. There were no reported adverse events or changes to vital signs following treatment with vaginal tamoxifen. The serum concentrations of vaginal tamoxifen were assayed after eight weeks of vaginal administration in all four treated subjects. Following a single dose of vaginal tamoxifen, there was noted to be a median plasma con-

centration of 5.8 ng/ml with a range of 1.0–10.0 ng/ml, taken approximately five hours after dosing (Table 2).

Discussion

VVA represents a significant health problem for postmenopausal women, including women who suffer from premature VVA as a result of breast cancer treatment. Every year, an increasing number of new cases of breast cancer are diagnosed among women in reproductive age. Many breast cancer survivors, especially young women, undergo menopausal symptoms, as direct consequences of cancer treatment [25]. Breast cancer patients treated with hormonal adjuvant therapy, particularly those using aromatase inhibitors refer to VVA as one of the most unpleasant side effects [26]. Published surveys on breast cancer survivors reveal that VVA has been reported to occur in 42% to 70% of postmenopausal patients [27]. Additionally, an alternative to estrogen therapy is needed for women who have a genetic predisposition to breast cancer.

Current low-dose vaginally administered estrogens are recognized as safe and effective treatment options for women with VVA. Local low-dose vaginal estrogens result in lower levels of circulating estrogen than oral or transdermal therapies. Recently, a 4-mcg estradiol dose was approved and noted to be the lowest dose available on the market, at a time where low-dose estrogen therapy is preferable [28]. Though, all estrogens, independent of dose delivered, contain an obligatory black box warning, flagging the risk of breast cancer. Therefore, an ideal treatment for VVA in high risk patients may be the use of vaginally administered tamoxifen therapy given its local estrogenic activity and systemic anti-estrogenic action.

The present exploratory study demonstrated that weekly vaginal administration of tamoxifen for three months in postmenopausal women with VVA is a possible new treatment approach. During the treatment, the objective measure of vaginal pH normalized similar to treatment using a low-dose estradiol vaginal capsule (4 mcg) given twice weekly after three months of treatment [29]. This study results suggests that local tamoxifen therapy is clinically meaningful compared with low-dose vaginal estradiol in normalizing vaginal pH. Also, vaginal tamoxifen reduced the severity of vaginal dryness at month 3 when compared to baseline. Vaginal dryness is voiced as the most bothersome problem in sexually active women who find coital activity uncomfortable because of inadequate lubrication [30]. In future investigational studies, vaginal maturation index (VMI) should be included as a co-primary endpoint to confirm/not confirm an estrogen-like effect with vaginal tamoxifen.

The application of vaginal dose of 20-mg tamoxifen directly provides clinical benefit without significant systemic absorption with median plasma concentration of 5.8 ng/ml with a range of 1.0–10.0 ng/ml. In comparison, after oral dose of 20-mg tamoxifen, the average steady state plasma concentration of tamoxifen after administration once daily for three months is 122 (range 71-183) ng/ml [31].

In conclusion, this exploratory study demonstrated that the administration of tamoxifen self-administered intravaginally clinically benefited women with symptoms of VVA. This was demonstrated through normalization of vaginal pH and improvement in vaginal dryness. Additionally, this route of administration provided meaningful clinical benefit without significant systemic absorption of the study drug. The robust local action of tamoxifen on the vaginal epithelium suggests that the parent compound itself is estrogenic and not metabolized locally in the vaginal epithelium, but predominantly systemically into anti-estrogens. Therefore, these results suggest that tamoxifen is an ideal drug candidate for the treatment of VVA in breast cancer risk patients given its local action as an estrogen and systemically as an anti-estrogen. Overall, study drug was well-tolerated and patients were generally satisfied with the product candidate as demonstrated by the low incidence of adverse events, adverse event discontinuations, ease of use, and high compliance with study and medication. Vaginal administration of tamoxifen to women with VVA may represent a treatment approach to patients at risk for breast cancer, and who have hormone-receptor-positive breast cancer, including estrogen receptor-positive (ER-positive) and progesterone receptor-positive (PR-positive), and node negative breast cancer. In view of the increasing demand for a safe treatment for VVA in breast cancer risk patients, further investigation of vaginal tamoxifen is warranted.

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