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Caution: Vaginal estradiol appears to be contraindicated in postmenopausal women on adjuvant aromatase inhibitors

A. Kendall[1], M. Dowsett[1], E. Folkerd[1] & I. Smith[2]*

[1]*Academic Department of Biochemistry and* [2]*Department of Medicine, Royal Marsden Foundation NHS Trust, London, UK*

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Background: Aromatase inhibitors (AI) are increasingly used in early breast cancer and there is a growing interest in associated long-term side-effects of profound estrogen suppression. Urogenital side-effects due to atrophic vaginitis are often managed with vaginal estrogen preparations. These are generally perceived to result in minimal systemic absorption of estrogen. We followed serum estradiol, follicle stimulating hormone (FSH) and luteinising hormone (LH) levels in seven postmenopausal women using vaginal estrogen preparations whilst on AIs for breast cancer.

Patients and methods: Serum was analysed for estradiol, FSH and LH at baseline then 2, 4, 7–10 and 12 weeks since commencement of vaginal estradiol. Estradiol was measured on an assay specifically developed for measuring low levels in postmenopausal women.

Results: Serum estradiol levels rose from baseline levels ≤5 pmol/l consistent with AI therapy to a mean 72 pmol/l at 2 weeks. By 4 weeks this had decreased to <35 pmol/l in the majority (median 16 pmol/l) although significant further rises were seen in two women.

Conclusions: The vaginal estradiol tablet Vagifem significantly raises systemic estradiol levels, at least in the short term. This reverses the estradiol suppression achieved by aromatase inhibitors in women with breast cancer and is contraindicated.

Key words: adjuvant, aromatase inhibitors, breast cancer, vaginal estrogen, hormone replacement therapy

introduction

Atrophic vaginitis is a significant problem in approximately 40% of postmenopausal women [1]. Associated dryness, pain, urinary incontinence and dyspareunia are consistently associated with marked deterioration in quality of life scores [2]. Postmenopausal women with breast cancer being treated with aromatase inhibitors (AI) can experience a worsening of these symptoms due to profound estradiol suppression [3]. As more women are living with metastatic breast cancer on AI therapy and these drugs move into the adjuvant setting, such side-effects are an increasing issue for patients and their physicians. Many women enquire whether topical vaginal estrogens can safely be used in this scenario. We have studied the effect of the vaginal estradiol tablet Vagifem on serum estradiol levels in a small number of women with severe atrophic vaginitis receiving adjuvant AI therapy.

Aromatase inhibitors exert their activity by inhibiting the enzyme aromatase that promotes the peripheral conversion of androgens to estrogens in postmenopausal women. AIs in current use inhibit the enzyme by >95% and reduce plasma estradiol levels from around 20 pmol/l to 3 pmol/l or less (the detection limit of the most sensitive assays). Several adjuvant AI studies in women with early breast cancer have now published extensive toxicity data. The Arimidex, Tamoxifen, Alone or in Combination (ATAC) Adjuvant Breast Cancer Trial reported vaginal dryness in 16.3% and dyspareunia in 17.8% of patients randomised to anastrozole alone compared with 8.4% and 7.5%, respectively, in the tamoxifen only group [4]. Conventional systemic estrogen replacement therapy to reduce symptoms is clearly contraindicated here. Vaginal estradiol preparations in the form of tablets, rings or creams are often offered as an alternative as they are perceived to have a low systemic absorption of estradiol. Vaginal estrogens have been shown to result in significant symptomatic benefit, which is superior to that of non-hormonal preparations. Vagifem vaginal tablet is commonly used due to good compliance and efficacy in treating atrophic vaginitis [5].

There are few published data on the absorption of estradiol levels secondary to Vagifem, although one study by Kvorning where Vagifem was administered at 25 mcg dose reported a peak at 80 pmol/l at 12 h, reducing to a steady state at <50 pmol after 14 h [6]. Notelovitz compared absorption from two doses of Vagifem in 58 women. Maximal and mean over 24 h concentrations of estradiol were 180 ± 99 pmol/l and

**Correspondence to:* Prof. I. Smith, Department of Medicine, Royal Marsden Foundation NHS Trust, Fulham Road, London SW3 6JJ, UK. Tel: +020-7808-2751; Fax: +020-7352-5441; E-mail: Ian.smith@rmh.nhs.uk

84 pmol/l for the 25 mcg dose and 81 ± 62 pmol and 40 pmol/l for the 10 mcg dose, respectively [7]. Higher serum levels of estradiol have been reported with other vaginal tablets and creams [8, 9]. To date no study has investigated the impact of vaginal estrogen preparations in women on aromatase inhibitors for treatment of their breast cancer. One cohort study of 1472 women previously treated for breast cancer found no statistically significant difference in the disease-free interval in a subgroup of women (4.7%) using vaginal estrogens (hazard ratio 0.57, 95% CI 0.2–1.58, $P = 0.28$). However, these women were not on AI adjuvant therapy and the small numbers of events in this study preclude a definitive result [10].

patients and methods

We prospectively measured the serum estradiol levels in six women on adjuvant AI therapy for early breast cancer who wished to take Vagifem for severe symptoms of atrophic vaginitis. The uncertainty of this approach was discussed with each and careful biochemical monitoring offered. All were prescribed Vagifem 25 mcg tablets administered daily for 2 weeks then twice weekly in accordance with manufacturer's recommendations. A further woman in our institution (patient seven) using Premarin vaginal estradiol cream whilst on anastrozole for metastatic breast cancer, was also monitored over a similar time course. Use of conventional estradiol assays in this group was not appropriate due to their inaccuracies in measuring serum estradiol levels <25 pmol/l [11]. Estradiol in serum was therefore measured by radioimmunoassay after ether extraction using an assay developed in our department to quantify low levels of estradiol found in postmenopausal women (sensitivity limit 3 pmol/l).

Serum estradiol, follicle stimulating hormone (FSH) and luteinising hormone (LH) were measured at baseline, then after 2, 4, between 7 and 10, and over 12 weeks after commencing Vagifem. After initial monitoring, venepuncture was generally planned to coincide with outpatient visits such that serum analysis was not possible at all time points in all of the women. FSH and LH were measured using an Immulite autoanalyser from Diagnostic Products Corporation (DPC, Los Angeles, USA).

results

The median age of the first six women in this study was 52 years (range 51–59). Five of the six women reported an improvement in their symptoms related to the use of Vagifem. All of the women (except one receiving exemestane) had initial serum levels of estradiol ≤5 pmol/l consistent with their AI therapy (Table 1). The steroidal aromatase inhibitor exemestane can interfere with the assay used to measure estradiol and may account for the higher than anticipated baseline value of 7.4 pmol/l seen in this woman [12]. At 14 days there was a rise in estradiol levels from a median of 3 to 72 pmol/l (range 3–232 pmol/l). By 28 days in the majority of the women there was a drop in estradiol levels to less than 35 pmol/l (median 16 pmol/l). However, random levels taken in two women who continued on Vagifem taken between weeks 7 and 10 revealed a further increase in levels of estradiol to 219 pmol/l and 137 pmol/l, respectively. Patient six, however, did not have a rise in estradiol levels despite compliance with the treatment. Patient seven who received a different vaginal estradiol preparation, Premarin, was also noted to have a similar pattern of estradiol levels with a marked increase in serum estradiol at 2 weeks, which had lowered by week 7.

FSH and LH levels were consistent with the postmenopausal status of women being investigated (Table 2). Throughout the period of treatment there was no appreciable intrasubject variability.

discussion

Our results show a significant rise in serum estradiol levels in the 2 weeks following commencement of Vagifem in six of the seven women, usually with a decrease after 1 month of therapy (Table 1, Figure 1) but with a return to pre-Vagifem levels in only two women after 7 and 12 weeks, respectively. Intersubject variability was high and reflects the difficulty of accurately measuring the low estradiol levels seen in women on AIs. FSH and LH were not seen to greatly change during the study.

Our experience in this small group of women on AIs and Vagifem raises concerns over the appropriateness of such a combination for effective breast cancer control since the efficacy of aromatase inhibition depends on near total suppression of estrogenic stimulation. The third generation inhibitors that inhibit aromatase by >97% are more effective in controlling breast cancer than earlier agents achieving only 90% inhibition [13], suggesting that even a small increase in systemic estrogen may be detrimental.

Table 1. Serum estradiol levels in women receiving concurrent aromatase inhibitors and Vagifem

Patient	Concurrent AI	Serum estradiol levels on Vagifem (pmol/l)				
		Baseline	Week 2	Week 4	Week 7–10	Week >12
1	Letrozole	<3.0	220	40	219	
2	Letrozole	<3.0	232	31	20	<3.0
3	Letrozole	3.5	77	16	3	
4	Anastrozole	<3.0	46		<3.0	<3.0
5	Exemestane	7.4	67	16	137	
6	Anastrozole	<3.0	<3.0	<3.0		
7[a]	Anastrozole	3.2	83		14	

[a]Patient 7 received Premarin vaginal estradiol cream in combination with anastrozole.

Table 2. Serum FSH and LH levels in women receiving concurrent aromatase inhibitors and Vagifem

Patient	Serum FSH and LH levels on Vagifem (IU/l)									
	Baseline		Week 2		Week 4		Week 7–10		Week > 12	
	FSH	LH	FSH	LH	FSH	LH	FSH	LH	FSH	LH
1	105	42	89	35	96	34	95	27		
2	155	65	123	53	118	45	124	56	126	58
3	59	31	52	28	57	36	79	34	61	33
4	107	32	94	37			116	32	92	34
5	138	48	138	48	124	46	135	44		
6	52	14	54	21	47	20				
7[a]	58	28	33	15			54	24		

[a]Patient 7 received Premarin vaginal estradiol cream in combination with anastrozole.

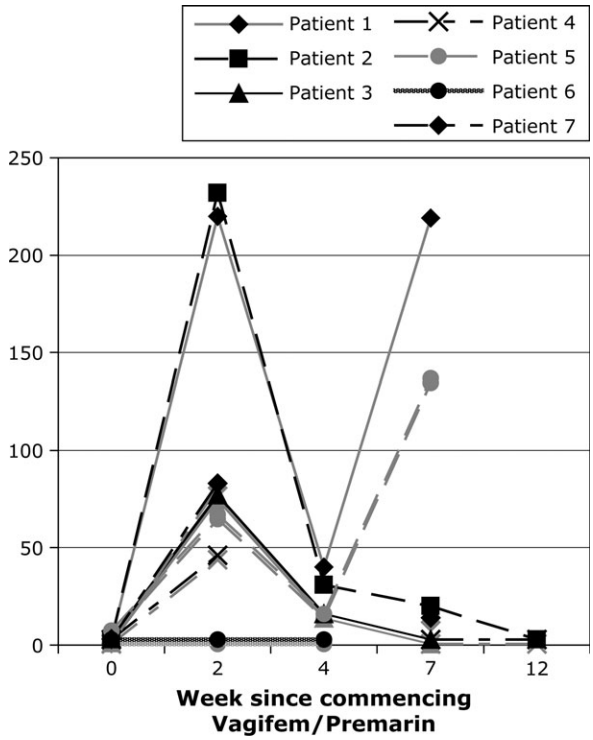

Figure 1. Serum estradiol levels in women receiving concurrent aromatase inhibitors and Vagifem.

The results suggest the possibility of a vaginal maturation effect during Vagifem therapy, which may gradually diminish absorption and therefore the systemic 'spill over' of estradiol. Nilsson et al. [14] reported similar findings in their study of 24 women receiving 10 and 25 mcg doses of Vagifem. Cytological and clinical evaluation of the vaginal and urethral epithelium were carried out. After 14 days of treatment maturation of the vaginal epithelium was seen with both regimens and the absorption of estradiol then declined significantly. Several groups have reported the estrogenic effect of tamoxifen on vaginal epithelium [15–17]. Findings suggest an early and persistant increase in vaginal maturation index following tamoxifen. It is therefore possible that the combination of vaginal estrogens and tamoxifen might provide a short-term interval option for women wishing to treat severe atrophic vaginitis, followed by a return to their usual AI therapy.

In conclusion, the vaginal estradiol tablet Vagifem used to treat symptoms associated with vaginal atrophy raises systemic estradiol levels in the short term. This effect reverses the estrogen suppression achieved by aromatase inhibitors in women with breast cancer and our view is that the combination is contraindicated, except in exceptional cases where regular monitoring of plasma estradiol by a laboratory with specialist assays with sensitivity for low estrogen values is available. Other non-hormonal preparations should be recommended for these patients [2].

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