The effect on climacteric symptoms of estrogen replacement therapy with an estradiol acetate intravaginal ring in postmenopausal women.

Introduction: Postmenopausal women commonly experience a range of climacteric symptoms, including hot flushes, nights sweats, loss of sexual interest and symptoms of anxiety and depression. This study evaluated climacteric symptoms in women treated with a novel intravaginal ring that delivers estradiol acetate and compared the effects to orally administered estradiol.

Methods: Women who had experienced at least 20 hot flushes or night sweats (HF/NS) for two consecutive weeks, were enrolled in this randomised, multicentre, double-blind study. The subjects were randomised to receive an intravaginal ring (IVR) releasing 50 µg/day estradiol acetate and placebo tablets (IVR group), or 1 mg/day oral estradiol and a placebo IVR (Oral group). Non-hysterectomised women received norethisterone (1 mg) for 12 days in each 28-day cycle.

Efficacy was measured by the mean change in HF/NS after 12 weeks' treatment, improvement in urogenital symptoms and changes in other climacteric symptoms, as assessed by the Greene Climacteric Scale. This scale has been validated in postmenopausal women and evaluates 21 symptoms, including loss of sexual interest and symptoms of anxiety and depression, the severity of each being reflected in a score of 0-3. The effects on scores in the Greene Climacteric Scale were recorded on Day 14 of each cycle.

Results: Both groups had significant ($p<0.001$) decreases in the frequency of HF/NS at 12 weeks. There was improvement in urogenital symptoms, including vaginal dryness, involuntary loss of urine and pain on intercourse, as measured by the intensity of symptoms and number of patients experiencing symptoms following both treatments. The IVR group had a significant ($p<0.05$) improvement in their Greene Climacteric Scale total scores, with a mean baseline score of 22.1 and mean score of 11.0 at 12 weeks. For every subscale, including anxiety, depression and sexual dysfunction, mean changes from baseline were also significant ($p<0.05$). There were no significant differences between the IVR and Oral groups at 12 weeks.

Conclusions: In addition to demonstrating a significant reduction in HF/NS, the IVR releasing estradiol acetate produced improvements in urogenital symptoms and other climacteric symptoms.
The improvement in climacteric symptoms was similar with the IVR and oral therapy.

Adapted from an abstract accepted by the British Menopause Society Meeting, June 28-29, 2001.

The Effect On Climacteric Symptoms of Estrogen Replacement Therapy With a Novel Estradiol Acetate Intravaginal Ring in Postmenopausal Women

H. Buckler[1] and W. Perry[2]

Department of Endocrinology, University of Manchester and Hope Hospital, Manchester, UK,[1] The Endocrine Centre, London, UK[2]

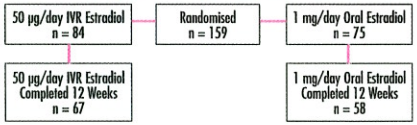
INTRODUCTION

- Postmenopausal women commonly experience a range of climacteric symptoms, including hot flushes (HF), night sweats (NS), sexual dysfunction, anxiety, and depression. Estrogens have been widely prescribed to control both the frequency and severity of these symptoms.
- Oral dosing is the most common method of administering estrogens. Other modes include transdermal patches, subcutaneous implants, topical gels, and a nasal spray.
- A silicone-based intravaginal ring (IVR) releasing low dose estradiol is also marketed. However, this product produces serum estradiol concentrations that are insufficient to treat vasomotor symptoms.
- A novel IVR (Menoring®/Galen Holdings) has been developed, which releases estradiol acetate at a rate equivalent to 50 µg of estradiol per day for 3 months.[1] Estradiol acetate is rapidly hydrolyzed in vivo to the naturally-occurring hormone estradiol. This IVR has been shown in clinical trials to produce significant improvement in vasomotor symptoms and urogenital symptoms in postmenopausal women.[1]
- This 12-week, prospective, double-blind, randomised, parallel group study compared the efficacy of an IVR delivering estradiol acetate versus orally administered estradiol. The results demonstrating efficacy in treatment of vasomotor and urogenital symptoms have been previously presented.[2] This analysis compares the effects of the two treatments on climacteric symptoms as measured by the Greene Climacteric Scale.[3]

METHODS

- Women <65 years of age who had experienced at least 20 hot flushes or night sweats (HF/NS) per week for 2 consecutive weeks were included. Subjects were randomised to treatment with an IVR releasing 50 µg/day estradiol and placebo tablets (IVR group), or oral therapy with 1 mg/day estradiol and a placebo IVR (oral group) (Figure 1). In both groups, women with an intact uterus also received 1 mg norethisterone for the last 12 days of each 28-day cycle (days 17 to 28) for the duration of the study.

Figure 1. Subject Disposition



- Subjects completed the Greene Climacteric Scale on Day 14 of each cycle, scoring the severity of each of the 21 symptoms on a scale of 0-3. Six sub-scale scores (psychological, anxiety, depression, somatic, sexual dysfunction, vasomotor) and one total score (all 21 items) were calculated for each subject at each timepoint. Subjects also completed daily diary cards assessing vaginal dryness, loss of urine, and pain on intercourse.
- The assessment of efficacy was the mean change in climacteric symptom scores from baseline to 12 and 24 weeks of treatment.
- Other assessments included safety, tolerability, and subject acceptability.

RESULTS

- Of 159 women enrolled, 84 (mean age 51.2 ± 5.4 years) were randomised to the IVR group and 75 (mean age 51.9 ± 5.3 years) to the oral group. A total of 71 women (45%) were post-hysterectomy.

Efficacy

- The IVR group as well as the oral group showed a significant ($P<0.05$) improvement in Greene Climacteric Scale total scores.
- The IVR group had a mean baseline total score of 22.1 and mean score of 11.0 at 12 weeks (Table 1). The oral group had a mean baseline total score or 22.3 and mean score of 10.8 at 12 weeks.

Table 1. Mean Greene Climacteric Scale Scores

	IVR Group		Oral Group	
	Baseline	12 Wks	Baseline	12 Wks
Total Score	22.1	11.0*	22.3	10.8*
Sub-Scales:				
Psychological	11.2	5.8*	11.4	5.6*
Anxiety	5.8	2.9*	6.2	2.8*
Depression	5.4	3.0*	5.2	2.8*
Somatic	4.6	3.1*	4.9	2.9*
Sexual dysfunction	1.7	1.0*	1.6	0.9*
Vasomotor	4.6	1.1*	4.5	1.3*

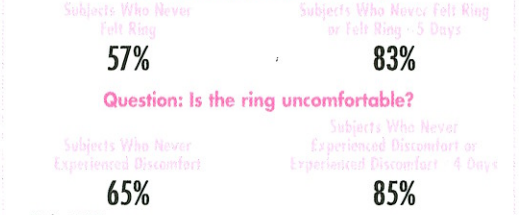
*$P<0.05$ vs baseline

- For every subscale including anxiety, depression, and sexual dysfunction, mean reductions from baseline in the IVR group were also statistically significant ($P<0.05$) (Table 1). There were no statistically significant differences between the IVR group and the oral group in any measure.

Subject Acceptability

- The IVR was well-accepted by subjects in the study. Most subjects were unable to feel the IVR and reported little discomfort (Figure 2).

Figure 2



n = 81 subjects in IVR group

- Similar results were observed in the oral group using the placebo IVR.
- Both the number of subjects reporting urogenital symptoms (vaginal dryness, involuntary loss of urine, and pain on intercourse) and the mean intensity of these symptoms decreased over the course of the study in the IVR group, as well as the oral group.

Safety

- The IVR was generally well tolerated. There were no significant differences in adverse effects between treatments. The most frequent adverse effects observed in both groups were headache and breast pain, as expected in women receiving systemic estrogen.
- No clinically important changes were noted during the general and vaginal examinations.

CONCLUSIONS

- A novel intravaginal ring delivering estradiol acetate is effective in producing a significant reduction in a wide range of climacteric symptoms throughout a 12-week period.
- Subject tolerability and acceptability of the estradiol IVR was excellent.
- No unexpected or serious local adverse events were reported.
- Overall, the safety and efficacy profile of the IVR in the treatment of climacteric symptoms of menopause was comparable to that of oral estradiol therapy.

REFERENCES

1. Data on file, Galen Holdings Plc.
2. Al-Azzawi F. Comparison of a novel intravaginal ring delivering estradiol acetate vs. oral estradiol for vasomotor symptom relief in postmenopausal women. Presented at the British Menopause Society, June 28-29, 2001, Birmingham, UK. Poster.
3. Greene JG. Constructing a standard climacteric scale. *Maturitas* 1998;29:25-31.

Adapted from a poster presented at British Menopause Society Meeting, June 28-29, 2001