Comparison of an intravaginal ring delivering estradiol acetate vs. oral estradiol for vasomotor symptom relief in postmenopausal women.

Introduction:

This prospective, double-blind, multicentre, randomised, parallel group study compared an intravaginal ring (IVR) delivering estradiol acetate for 90 days to orally administered estradiol for efficacy in treating vasomotor symptoms.

Methods:

Women who had experienced at least 20 hot flushes or night sweats (HF/NS) of any severity for 2 consecutive weeks, were randomised to treatment with either the IVR (equivalent to 50 µg estradiol/day) or oral therapy (1 mg estradiol/day). The frequency of vasomotor symptoms was captured in diary cards, which were completed daily. The primary assessment of efficacy was the mean change in the number of HF/NS after 12 weeks' treatment.

Results:

159 women were enrolled in the study; 85 were randomised to the IVR group and 75 to the oral group. The mean ages of the women were 51.2 (SD±5.4) years for the IVR group and 51.9 (SD±5.3) years for the oral group. 71 (45%) of the women had had a hysterectomy. The average frequency of the HF/NS per week reported at baseline was 57.2 (SD±41.4) for the IVR group and 55.0 (SD±33.8) for the oral group. At 12 weeks, both treatments resulted in significant ($p<0.001$) decreases to 9.1 (SD±12.1) HF/NS per week in the IVR group (84% decrease from baseline) and 15.0 (SD±19.4) HF/NS per week in the oral group (73% decrease from baseline). The differences between treatments were not statistically significant. The IVR and oral therapies were well tolerated. Overall, the adverse effects seen in this study were those expected in women receiving systemic estrogen (headache, breast tenderness and nausea) and were similar for both groups.

Conclusions:

These results show that this intravaginal ring delivering estradiol acetate is effective throughout the three months of treatment, with 93% of subjects reporting a >50% reduction and 59% of subjects reporting a >80% reduction in their frequency of HF/NS after 12 weeks' treatment. Overall, the safety and efficacy profile of the IVR was comparable to that of oral therapy.

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Comparison of a Novel Intravaginal Ring Delivering Oestradiol Acetate vs. Oral Oestradiol for Vasomotor Symptom Relief in Postmenopausal Women

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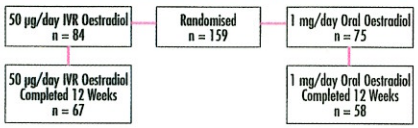
INTRODUCTION

- Oestrogens are widely prescribed to treat hot flushes (HF) and night sweats (NS) in postmenopausal women.
- Oral dosing is the most common method of administering oestrogens. Oral oestradiol is subject to substantial first pass metabolism, resulting in a reduction in the oral bioavailability to less than 20%.[1] Other modes of delivering systemic oestrogen include transdermal patches, subcutaneous implants, topical gels, and nasal sprays.
- Local oestrogen therapy is available as vaginal creams, tablets, and an intravaginal ring (IVR) releasing low-dose oestradiol. These treatments do not deliver sufficient oestrogen to effectively treat vasomotor symptoms, and are indicated only for the treatment of local urogenital symptoms.
- A novel IVR (Menoring®/Galen Holdings) has been developed that releases oestradiol acetate at a rate equivalent to 50 µg of oestradiol per day for 3 months.[2] Oestradiol acetate is rapidly hydrolysed in vivo to the naturally-occurring hormone oestradiol.
- This novel IVR has been designed to allow treatment of vasomotor and urogenital and other climacteric symptoms.
- This 12-week, prospective, double-blind, randomised, parallel group study compared an IVR delivering oestradiol acetate for 3 months versus orally administered oestradiol for efficacy in treating vasomotor symptoms.

METHODS

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

Figure 1. Subject Disposition



- The primary assessment of efficacy was the mean change in the number of hot flushes or night sweats (HF/NS) after 12 weeks of treatment, as self-reported by subjects on daily diary cards.
- Secondary assessments included safety and acceptability, and systemic and local vaginal tolerability of the ring.

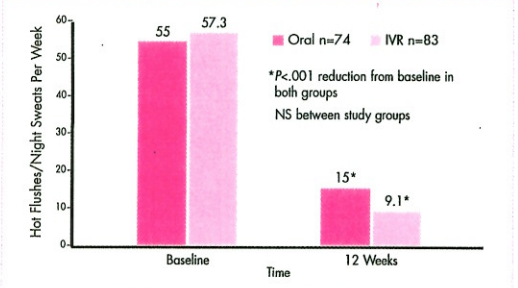
RESULTS

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

EFFICACY

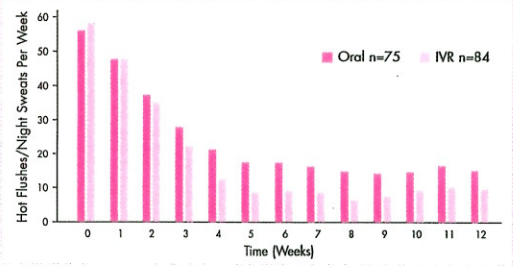
- At baseline, the average frequency of HF/NS reported by subjects in the IVR group was 57.2 ± 41.4 per week versus 55.0 ± 33.8 per week for subjects in the oral group. At 12 weeks, the average frequency of HF/NS was significantly reduced ($P<0.001$) in both treatment groups (Figure 2), reaching 9.1 ± 12.1 per week in the IVR group (84% decrease from baseline) and 15.0 ± 19.4 per week in the oral treatment group (73% decrease). The difference between treatment groups was not statistically significant.

Figure 2. Effect of IVR or Oral Oestradiol on the Frequency of Vasomotor Symptoms at Baseline, 12 Weeks, and 24 Weeks



- In both treatment groups, the reduction in the frequency of HF/NS was sustained throughout the treatment period and did not show a reduction in efficacy up to the end of the study (Figure 3).
- At 12 weeks, HF/NS relief was similar in both groups.

Figure 3. Effect of IVR and Oral Oestradiol on the Weekly Frequency of Vasomotor Symptoms



- At 12 weeks, 56% (40/71) of evaluable IVR subjects and 52% (34/65) of evaluable oral subjects reported 100% relief, and 59% (49/83) of IVR subjects and 65% (48/74) of oral subjects reported >80% relief.

SAFETY

- Both IVR and oral therapy were well tolerated. Overall, the most frequent adverse effects (AEs) observed in both groups were similar to those reported previously in women receiving systemic oestrogen (headache and breast pain) (Table 1).

Table 1. Incidence of Most Common Adverse Events (0 to 24 Weeks)

ADVERSE EVENTS	IVR GROUP n (%)	ORAL GROUP n (%)
Headache	41/84 (48.8%)	30/75 (40.0%)
Vaginal discharge	16/84 (19.0%)	11/75 (14.7%)
Nausea	16/84 (19.0%)	10/75 (13.3%)
Abdominal distension	11/84 (13.1%)	11/75 (14.7%)
Breast tenderness	11/84 (13.1%)	7/75 (9.3%)
Arthralgia	10/84 (11.9%)	14/75 (18.7%)
Dizziness	10/84 (11.9%)	8/75 (10.7%)
Breast pain	9/84 (10.7%)	5/75 (6.7%)
Back pain	9/84 (10.7%)	16/75 (21.3%)
Abdominal pain	9/84 (10.7%)	10/75 (13.3%)

- The frequency of AEs reflects the use of subject diary cards to collect AEs on a daily basis.
- A total of 25 subjects (16%), 16 from the IVR group and 9 from the oral group, withdrew from the study due to adverse events. The type, frequency, and severity of such events were similar for subjects treated with IVR and oral oestradiol.
- During treatment, there was evidence of general improvement in signs related to vaginal atrophy. No clinically important changes were noted during the general and vaginal examinations (Table 2). No changes were observed in vaginal or cervical cytology.

Table 2. Vaginal Examination Findings at Baseline and 12 Weeks

VAGINAL FINDING	IVR GROUP		ORAL GROUP	
	Baseline n (%)	12 weeks n (%)	Baseline n (%)	12 weeks n (%)
Epithelial redness	6/84 (7%)	0/66 (0%)	14/75 (19%)	0/57 (0%)
Inflammation	1/84 (1%)	0/66 (0%)	2/75 (3%)	0/58 (0%)
Granulation	0/84 (0%)	0/67 (0%)	0/75 (0%)	0/58 (0%)
Vaginal ulceration*	0/84 (0%)	0/67 (0%)	0/75 (0%)	0/58 (0%)
Vaginal discharge	7/84 (8%)	5/66 (8%)	3/75 (4%)	7/57 (12%)
Other**	3/83 (4%)	0/65 (0%)	7/75 (9%)	4/57 (7%)

*1 vulvular ulceration was noted.
**Consists mainly of vaginal wall weakness, cervical polyps and cervical ectropian.

- Subjects' assessment of vaginal symptoms and acceptability of the ring indicated that the ring was well tolerated and accepted.

CONCLUSIONS

- A novel intravaginal ring delivering controlled amounts of oestradiol acetate is effective in producing a significant reduction in menopausal vasomotor symptoms throughout the 3-month oestradiol delivery period.
- Tolerability of the oestradiol IVR was shown to be favourable, with excellent subject acceptability. No unexpected or serious local adverse events were reported.
- Overall, the safety and efficacy profile of the IVR was comparable to that of oral therapy, and in keeping with that expected with oestradiol therapy.

REFERENCES

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