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Pharmacokinetic and tolerability study of a novel 17β-estradiol and progesterone intravaginal ring in sheep

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PURPOSE

To evaluate the pharmacokinetics and local tolerability of a novel, segmented ethylene-vinyl acetate (EVA) intravaginal ring (IVR) delivering 17β-estradiol (E2) and progesterone (P), in drug-naïve ovariectomized female Dorset crossbred sheep. This IVR, called DARE-HRT1, is being developed to treat vasomotor symptoms (VMS).[1] The product may also provide effective treatment of genitourinary symptoms associated with vulvovaginal atrophy (VVA). Similar EVA-based IVRs have been evaluated clinically.[2]

METHODS

IVRs were prepared by hot-melt extrusion to create segments of varying length and drug content. Segment drug loading and length were used to create IVRs by thermal welding with the following target release rates: 160 µg/d E2 with 4 or 8 mg/d P over 28 d. Release rates of E2 and P from the two IVR formulations were measured in vitro. Release rates were tested under sink conditions at 37°C. Sheep were randomized to one of 5 treatment groups: 1) 50 µg/d E2 reference IVR (Femring®)(*n* = 3); 2) 100 µg/d E2 reference IVR (Femring)(*n* = 3); 3) EVA IVR 160 µg/d E2 with 4 mg/d P (*n* = 5), 4) EVA IVR 160 µg/d E2 with 8 mg/d P (*n* = 5); and 5) 160 µg E2 and 10 mg P intravenously (*n* = 3). IVRs were placed on Day 1 and remained in place through Day 29. Animals underwent daily examinations vaginal irritation [0 (none) to 4 (severe)]. Blood samples were taken at scheduled times for pharmacokinetic (PK) analysis. Postmortem examinations included clinical observations and external vaginal irritation assessment, and macroscopic and microscopic evaluations of the female reproductive system.

RESULTS

Following burst release of both drugs over Day 1, the experimental IVRs released E2 and P in vitro at the desired average rates from Day 2 through 28 (Figure 1). IVRs remained in place over the 28-d study with the exception of one animal. Following removal of the IVRs on Day 29, analysis of the residual E2 and P remaining in the IVRs showed that all rings were within ± 10% of the theoretical mass balance of both hormones, with the exception of the ring obtained from the Group 4 animal that had a replacement IVR on Day 18. Plasma concentrations of E2 and P from all IVRs tested are sown in Figure 2. PK parameters (Tables 1 and 2) were generally those expected based on the in vitro dissolution of E2 and P from the EVA IVRs. C_{AVG} for E2 was similar in the EVA IVR animals (25.9 ± 3.2 and 31.3 ± 5.3 pg/mL); the C_{AVG} of P was approximately doubled when comparing the 4 and 8 mg/d EVA IVRs (357 ± 11.2 and 722 ± 94.1 pg/mL, respectively). Clinical observations showed no significant abnormal findings. Microscopic observation showed changes in the EVA IVR groups, which were more frequent in the cranial vagina. Assessment of the vaginal irritation index according to the method of Eckstein showed minimal irritation in all treatment groups, with irritation scores typically highest (but still minimal to mild) in the cranial portion of the vagina where the IVR was placed.

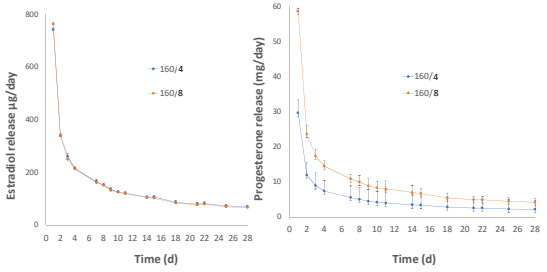

Figure 1. In vitro release of E2 (left) and P (right) from DARE-HRT1 IVRs releasing 160 µg/d E2 and 4 mg/d or 8 mg/d P. Data are means ± SD (n = 6).

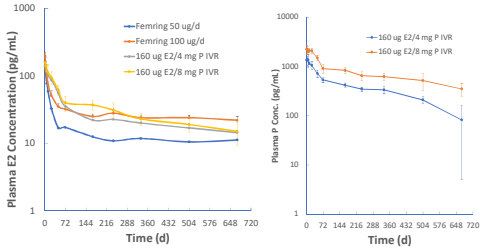

Figure 2. Plasma concentration-time profiles of E2 (left panel) following a single intravaginal insertion of comparator IVRs (Femring 50 or 100 µg/d) and DARE-HRT1 (160 µg/d E2 in combination with 4 mg/d or 8 mg/d P) and P (right panel) from DARE-HRT1 (160 µg/d E2 in combination with 4 mg/d or 8 mg/d P). Data are means ± SD (n = 5).

Table 1. E2 PK parameters from Femring and DARE-HRT1 IVRs

PK Parameter	Group 1 50 µg/d E2 (Femring)	Group 2 100 µg/d E2 (Femring)	Group 3 DARE-HRT1 160 µg/d E2 & 4 mg/d P	Group 4 DARE-HRT1 160 µg/d E2 & 8 mg/d P
C_{max} (pg/mL)	164 ± 26.8[a]	197 ± 29.6	149 ± 21.3	158 ± 54.6
$AUC_{0\text{-}672\ h}$ (h*pg/mL)	9,690 ± 1,750	19,000 ± 1,170	17,400 ± 2,120	21,000 ± 3,540
C_{AVG} (pg/mL)	14.4 ± 2.6	28.2 ± 1.75	25.9 ± 3.16	31.3 ± 5.26
R_0 (µg/d)	31.0 ± 5.6	60.8 ± 3.8	55.9 ± 6.8	67.3 ± 11.3

[a]Data are means ± SD (*n* = 5)
[b]R_0 = calculated in vivo release rate

Table 2. PK parameters of P from DARE-HRT1 IVR Groups (3 & 4)

PK Parameter	Group 4 4 mg/d	Group 4 8 mg/d
C_{max} (pg/mL)	1,590 ± 272	2,400 ± 322
$AUC_{0\text{-}672\ h}$ (h*pg/mL)	240,000 ± 7,510	485,000 ± 63,200
C_{AVG} (pg/mL)	357 ± 11.2	722 ± 94.1
R_0 (µg/d)	3,523 ± 112	7,132 ± 932

The vaginal tolerability of the DARE-HRT1 IVRs was assessed. The vaginal irritation according to the method of Eckstein[3] showed minimal irritation in all treatment groups, with irritation scores typically highest in the cranial portion of the vagina where the IVR was placed.

CONCLUSIONS

This study demonstrated the safety and tolerability of a novel EVA E2/P combination IVR in a relevant animal species. The DARE-HRT1 IVRs were well tolerated with demonstrable release profiles of both E2 and P that are projected to be efficacious and with comparable bioavailability to currently marketed products. These results support the progression of this combination product into human clinical studies.

References

1. Hamada, et al., *Gynecol Endocrinol*, **17** 247-254 (2003)
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3. Eckstein, et al. *J Reprod Fertil* **20** 85-93 (1969)

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