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Pharmacokinetics and tolerability of a novel progesterone intravaginal ring in sheep

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PURPOSE

To evaluate the in vitro release and in vivo pharmacokinetics and local tolerability of a novel, segmented ethylene-vinyl acetate (EVA) intravaginal ring (IVR) delivering progesterone (P) in drug-naive female ovariectomized Dorset crossbred sheep. These IVRs (DARE-FRT1) are being developed to the prevention of preterm birth in singleton pregnancies in women with short cervical length.[1,2] Similar EVA-based IVRs have been evaluated clinically.[3]

METHODS

IVRs were prepared by hot-melt extrusion to create segments of varying length and drug content. IVRs releasing P at rates of approximately 4, 8, and 12 mg/day. Release rates of P from the three IVR formulations were measured in vitro. Release rates were tested using 200 mL 0.5% sodium dodecyl sulfate as a release medium, in shakers at 37°C. Animals were randomized into one of six treatment groups: Group 1) Crinone® 8% gel (90 mg); group 2) Prometrium® 200 mg capsules; group 3) placebo IVR; group 4) P IVR 4 mg/day; group 5) P IVR 8 mg/d, or group 6) P IVR 12 mg/d. IVRs were inserted intravaginally on Day 1 and replaced on Day 15. Blood samples were taken at scheduled times prior to and following the first insertion for pharmacokinetic (PK) analysis from Days 1 to 14. Concentrations of P in plasma were measured using a validated LC-MS/MS method. Evaluations on all IVR groups included clinical observations and external vaginal irritation assessment and macroscopic and microscopic evaluations of the female reproductive system, including internal vaginal irritation scoring.

RESULTS

- Following a burst release on Day 1, in vitro data confirmed that P was released with an average of 4, 8, or 12 mg/d over Days 2 – 14 for each of the IVR experimental dose groups (see Figure 1).
- IVRs were retained over 28 days in all animals with two exceptions. PK analysis in animals showed sustained release of P from Days 0 through 14 of ring use (see Figure 2). Following removal of the IVRs on Day 14 analysis of the residual P remaining in the IVRs showed that all rings were within ±10% of the theoretical mass balance.
- PK parameters (Tables 1 and 2) from the three different IVRs were consistent with the in vitro release rates. C_{avg} increased in a dose-related manner, with mean values of 455, 682, and 1,040 pg/mL for the 4, 8 and 12 mg/day IVR groups, respectively. The lower dose Crinone gel (90 mg P) showed substantially greater relative bioavailability compared with the higher dose Prometrium capsules (200 mg P).
- No EVA IVR-related effects on bodyweights, clinical observations, vaginal irritation, and macroscopic or microscopic pathology of reproductive tissues were noted. Irritation scores and microscopic assessments demonstrated minimal to mild local irritation and were consistent with foreign body placement in the vaginal vault (see Table 3).

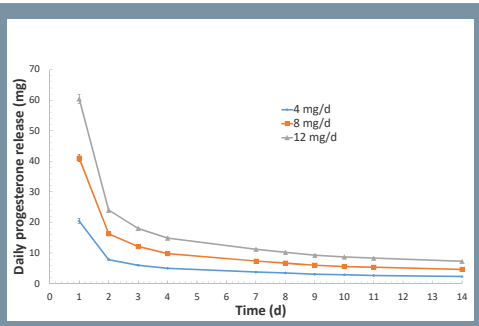

Figure 1. In vitro release of P from DARE-FRT1 IVRs (4 mg/d, 8 mg/d, and 12 mg/d). Data are means ± SD (n = 6).

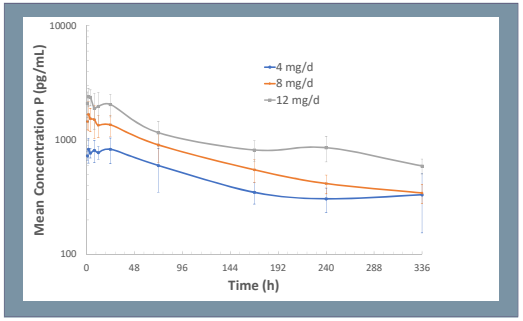

Figure 2. Plasma concentration-time profiles of P from Day 0 through Day 14 following a single administration of DARE-FRT1 IVRs releasing P at 4 mg/d, 8 mg/d, and 12 mg/d. Data are means ± SD (n = 5).

Table 1. PK parameters from Crinone 8% gel (90 mg) and Prometrium 200 mg capsules

PK Parameter	Group 1 90 mg P Gel[a]	Group 2 200 mg P Capsule[b]
C_{max} (pg/mL)	3,020 ± 140	1,390 ± 206
$AUC_{0\text{-}24\ h}$ (h*pg/mL)	20,700 ± 1,640	12,000 ± 4,090
C_{AVG} (pg/mL)	863 ± 68.5[c]	501 ± 170
T_{max} (h)	2 (2-4)[d]	2 (2-2)

[a]90 mg dose of P is approximately 1.5 mg/kg based on a 60 kg sheep
[b]200 mg dose of P is approximately 3.3 mg/kg based on a 60 kg sheep
[c]$C_{AVG} = AUC_{0\text{-}24\ h}/24$ h
[d]Median (minimum – maximum), median value only reported if actual collection interval

Table 2. PK parameters of P from DARE-FRT1 IVR Groups (4, 5, and 6)

PK Parameter	Group 4 4 mg/d	Group 5 8 mg/d	Group 6 12 mg/d
C_{max} (pg/mL)	969 ± 145	1,820 ± 469	2,520 ± 432
$AUC_{0\text{-}24\ h}$ (h*pg/mL)	153,000 ± 38,900	229,000 ± 407,000	350,000 ± 73,900
C_{AVG} (pg/mL)	455 ± 116	682 ± 121	1,040 ± 220
T_{max} (h)	12 (1 – 72)[a]	2 (1 – 8)	4 (2 – 8)

[a]Median (minimum – maximum), median value only reported if actual collection interval

Table 3. Collective group mean IVR vaginal irritation scores

Vaginal Location	Placebo (Group 30	4 mg/d (Group 4)	8 mg/d (Group 5)	12 mg/d (Group 6)
	n = 3	*n* = 5	*n* = 5	*n* = 5
Cranial	1.67	-0.47	-0.67	-0.47
Mid	1.00	0.20	0.00	0.20
Uro	1.33	-0.13	-0.33	-0.53

CONCLUSIONS

The data obtained from this study demonstrate that the segmented EVA IVRs are capable of sustained in vivo release of P at varying rates over a 14-day period. The DARE-FRT1 IVRs showed little signs of vaginal irritation or mucosal breaches. These results support the conclusion that the EVA P releasing IVRs are suitable for evaluation in a Phase 1 clinical study in women.

References

1. Fonseca, et al., *New Engl J Med*, **357**(5) 462-469 (2007)
2. Hassan, et al., *Ultrasound Obstet Gynecol*, **38**(1) 18-31 (2011)
3. Kimball, et al., *J Controlled Rel,* **233** 19-28 (2016)

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