

Development of a silicone-based intravaginal letrozole-releasing device for synchronization

E.M. Zwiefelhofer ^a, B.M. Davis ^a, G.P. Adams ^{a*}

^a Department of Veterinary Biomedical Sciences, Western College of Veterinary Medicine, University of Saskatchewan, Saskatoon, Saskatchewan, Canada S7N 5B4

*Corresponding Author: 52 Campus Drive, WCVI, Saskatoon, Saskatchewan, Canada S7N 5B4 Phone: 306 966 7411; e-mail: gregg.adams@usask.ca

Two experiments were conducted to test the effectiveness of a silicone matrix as an intravaginal drug delivery device for letrozole, an aromatase inhibitor used in a novel synchronization protocol for cattle. Results of previous studies documented that intravaginal delivery of letrozole was superior to other routes of delivery in cattle, but the wax dip-coat formulation of the intravaginal device was cumbersome to manufacture and deploy, resulting in unwanted variation in drug delivery and circulating concentrations of letrozole. In Experiment 1, a 3 x 3 design was used to test the release kinetics of letrozole from silicone *in vitro*. Silicone was mixed with 3 different letrozole drug loads (5%, 10%, 15%) and 3 different mineral oil loads (5%, 10%, 15%), and letrozole release into 63% ethanol was compared with the wax dip-coat formulation (positive control) by UV spectrophotometry. Letrozole was released from silicone in a dose-dependent manner, with no effect of mineral oil. Release kinetics were then examined *in vivo* (Experiment 2) in nulliparous beef heifers assigned randomly to six groups (n=6/group) and given an expanded or conventional intravaginal silicone device impregnated with a medium or high drug load, or a wax dip-coat device (positive control) or blank device (negative control). Devices were inserted on Day 3 (Day 0=ovulation) and remained in place until Day 11. Blood samples were collected at 0, 30 mins, 1, 2, 3, 4, 6, 8, 10, 12, and 24 hours, and twice daily until Day 11 to determine plasma concentrations of letrozole by LC-MS/MS. The ovaries were examined once daily by ultrasonography to determine follicular and luteal responses to treatment. Plasma concentrations of letrozole were higher in heifers with an expanded vs conventional silicone device ($P<0.05$) and those with a device with high vs medium drug-load ($P<0.05$). With respect to ovarian function, the follicular inter-wave interval was similar and longest ($P<0.05$) in the positive control and the expanded high-load silicone groups. Similarly, the diameter profiles of the dominant follicle and corpus luteum were largest ($P<0.01$) in the positive control and the expanded high-load silicone groups. There was a strong correlation ($r=0.45$; $P<0.0001$) between letrozole concentration and follicle growth. In conclusion, letrozole was released from a silicone matrix in a dose-dependent manner, and expanded high-load devices achieved target effects on ovarian function. Results may be used to manufacture a silicone intravaginal device for delivering aromatase inhibitors in a novel synchronization protocol for dairy cattle.