Pharmacokinetics of oral micronized progesterone and intravaginal progesterone administration in the bitch

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The aim of this study was to determine the pharmacokinetics (PK) of vaginally (Crionone®, Serono Laboratories, Norwell, MA) and orally delivered micronized progesterone (Prometrium®, Solvay Pharmaceuticals, Inc., Marietta, GA) in the bitch. We hypothesized that both vaginal and oral treatments would result in a dose-dependent increase in concentrations of plasma progesterone. We further hypothesized that oral dosing of micronized progesterone would result in greater, sustained plasma progesterone than those recorded in bitches treated with intravaginal (IVA) micronized progesterone gel. Eight adult sexually intact bitches in anestrus were arranged in a 4x4 Latin square with repeated measures experimental design. Each subject rotated through four different progesterone treatment groups with a minimum seven day-wash out period between treatments: 100 mg oral micronized progesterone, 200 mg oral micronized progesterone, 45 mg intravaginal micronized progesterone and 90 mg intravaginal micronized progesterone. Blood samples from each subject were obtained at time points 0, 0.5, 2, 1.5, 2, 4, 6, 8, 12, 24, 36, 48 and 72 hs following treatments. Concentrations of plasma progesterone were determined by RIA (ImmuChem Double Antibody, 125I RIA Kit, MP Biomedicals, Costa Mesa, CA). Pharmacokinetic analysis was carried out using commercially available software (Phoenix WinNonlin 6.4, Certara Inc., Princeton, NJ). One-compartmental (intravaginal) and non-compartmental (oral administration) modeling were performed to analyze data using the mean concentrations for each dosing to calculate the area under the curve (AUC), maximum plasma concentration (Cmax), time elapsed to reach Cmax (Tmax), and elimination half-life (~t1/2).

Results for the 100 mg and 200 mg oral doses and 45 mg and 90 mg IVA doses were as follows: AUC, 30.86, 187.96, 90.64, and 226.68 ng.h.ml⁻¹, respectively; Cmax, 13.47, 169, 8.68, and 13.24 ng.ml⁻¹, respectively; Tmax, 0.5, 0.5, 0.84, and 1.67 hs, respectively, and half-life, 5.87, 6.76, 6.6, and 10.65 hs, respectively.

Micronized progesterone was readily absorbed in bitches when administered either orally or intravaginally. Contrary to our initial hypothesis, the extent of body exposure to progesterone as indicated by the area under the curve was greater when intravaginal micronized progesterone was used. The ability of intravaginal preparations of micronized progesterone to induce sustained progesterone exposure may provide an alternative strategy for treating pregnant dogs whenever hypoluteoidism is being suspected.

Keywords: Micronized progesterone, pharmacokinetics, canine