Pharmacokinetics of intra-rectal altrenogest administration in horses

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Hospitalized high-risk pregnant mares being held nil per os (NPO) due to medical or surgical events present a dilemma for multi-modal therapy aimed at pregnancy maintenance, which commonly includes oral altrenogest as the supplemented progestin. Some long-acting intramuscular preparations do not reach peak concentrations until 24 h after administration and repeated IM injections can cause severe complications, such as abscess formation and clostridial myonecrosis. Rectal administration of medications is a recognized route for achieving systemic concentrations, but there are currently no data available on the pharmacokinetics of rectal altrenogest administration in horses. The purpose of this study was to determine the pharmacokinetics of altrenogest following per os (PO) or per rectum (PR) administration in mares. Using a randomized two-way crossover study design, six horses received altrenogest (0.088 mg/kg; PO or PR q 24 h for 5 d), with a 7- day washout period. Plasma samples were collected prior to administration (0 h) and at 0.25, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12, 24, 48, 72, 96.0, 96.25, 96.5, 97.0, 97.5, 98.0, 98.5, 99.0, 100, 102, 104, 108, 112, 120, 144, 168, and 192 h after administration. The concentrations of altrenogest were determined by ultra-high performance liquid chromatography with tandem mass spectrometry. Assay validation and quality assurance were performed according to published guidelines. Administration PR produced therapeutic plasma levels in all mares following initial dosing (C_{max} 2.54 $\pm$ 1.18 ng/mL) with a markedly decreased time to maximum concentration (T_{max} 0.83 $\pm$ 0.26 h) when compared to PO administration (T_{max} 4.25 $\pm$ 4.83 h). Plasma concentrations only persisted above presumed therapeutic concentrations (0.5 ng/mL) for a mean of 5.5 h (range 3-8 h) following PR administration, while serum concentrations remained > 0.5 ng/mL for at least 24 h in all horses following PO administration. The calculated half-life (T½) of PR administration (2.82 $\pm$ 1.07 h) was correspondingly decreased when compared to PO administration (7.01 $\pm$ 3.13 h). Relative bioavailability of altrenogest following PR administration was only 5.47%. In conclusion, altrenogest is rapidly absorbed following PR administration in the horse and reaches therapeutic concentrations, making this a viable method of treatment in NPO mares. However, the decreased bioavailability and shorter detection time would require a shorter dosing interval. Results of this study suggest 0.088 mg/kg PR q 4-8 h would be necessary to maintain therapeutic concentrations over a 24 h period.

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