

## ADMINISTRATION OF ORAL SUSTAINED-RELEASE TABLET FORMULATION OF TRAMADOL IN HORSES: PHARMACOKINETICS OF THE PARENTAL DRUG AND OF N-DESMETHYLTRAMADOL

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In humans sustained-release tablet formulation (SRTF) of tramadol allows gradual release of the active drug, permitting once-daily administration. This formulation has been demonstrated to be equivalent in bioavailability to immediate release tramadol administered four times daily, with prolonged absorption and lower peak plasma concentrations (1). In dogs, rabbits, guinea pigs, rats, hamsters and mice (2) tramadol half-life was shorter than in human being and it was metabolized much more rapidly than in humans. The aim of the present study was to evaluate the pharmacokinetics of tramadol and its metabolite N-desmethyltramadol in horses after administration of oral SRTF. It has been previously observed that after tramadol iv administration in horses severe adverse events (dizziness, vertigo, respiratory depression, hypo-hypertension, seizures and/or hallucinations) have been reported and immediate release tramadol has in horses an half life four folds faster than in human beings. Six horses (male, 8-10 years old, weighing 470-540 kg) were administered with tramadol 5 mg/kg (Contramal sustained release tablets 100 mg/tablet) *via* naso-gastric tube in fasting status. After drug administration naso-gastric tube was then rinsed with 500 mL of water to ensure complete delivery of the drug into the stomach. An indwelling catheter was inserted into the jugular vein of the animals to allow blood withdrawals at the following times: 0, 0.083, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 24, 28 and 36h. Plasma concentrations of tramadol and N-desmethyltramadol were measured by HPLC apparatus with fluorimetric detection (3). SRTF permitted to obtain a gradual release up to 24 h with a C<sub>max</sub> of 0.043±0.01 µg/ml and a T<sub>max</sub> of 4.46 h. Half life was 3.43±0.51 h, Cl 11.49±1.42 l/h kg, AUC 0.47±0.06 µg h/ml and the bioavailability 10.5%. These data show a faster kinetics of tramadol SRTF in comparison with a human SFTR study (4) where T<sub>max</sub> was about 10 h and the half life 8 h. After 30 min from drug administration, the concentration of inactive metabolite N-desmethyltramadol (5) higher than that of its parenteral drug tramadol, which remains constant and low, suggest that in horses this formulation could be less active than in humans. This hypothesis is also supported by tramadol SRTF low bioavailability.

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