PHARMACOKINETICS OF TRAMADOL AND OF ITS METABOLITE N-DESMETHYLTRAMADOL IN FASTING AND FED HORSES, AFTER SINGLE ORAL ADMINISTRATION

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Tramadol is a centrally-acting analgesic drug used in the treatment of mild to moderate pain. It is administered in a large therapeutic range among different animal species and it can sometimes exhibit severe adverse effects, such as respiratory depression, hypo-hypertension, seizures and/or hallucinations. Clinical response to tramadol is strictly correlated to its metabolism, because of the different amount of its active metabolite reported in different animal species (1). Therefore, the evaluation of plasma concentrations and the metabolism of tramadol in horses are important points to avoid side effects. In the present study twelve male animals, 7-10 years old, weighing 460-540 kg were randomly used. Six horses, fasted for at least 10 h (food) and 3 h (water) before and after dosing, were administered orally with tramadol 5 mg kg (Exal 50 mg/capsule) and six horses were administered orally with tramadol 5 mg kg (Exal 50 mg/capsule) with food and water *ad libitum*. To allow withdrawals of heparinized blood sample at the following times 0, 0.083, 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, and 24h an indwelling catheter was inserted into the jugular vein of the animals. Plasma concentrations of tramadol and N-desmethyltramadol were measured by HPLC apparatus with fluorimetric detection (2). After tramadol administration pharmacokinetic parameters of the parental drug in fasting and fed horses resulted of 1.77±0.22 and 3.61±0.50 μg/ml in Cmax, 0.42±0.08 and 0.33±0.11 h in Tmax, 1.03±0.10 and 1.92±0.27 h in $T_{1/2}$, 1.75±0.33 and 0.81±0.31 μg h/ml in AUC, 1.86±0.25 and 0.75±0.12 l/kg in Vd, 1.80±0.22 and 1.43±0.27 l/h kg in Cl and 64.5±8.36 and 84.6±18.35 % in bioavailability, respectively. The pharmacokinetics of tramadol resulted faster in horses than in humans (3), suggesting that 4 daily administration are needed to maintain drug plasma concentrations clinically effective within 24 hours. Moreover in horses, the intake of food seems to affect significantly only pharmacokinetic parameters as Cmax and $T_{1/2}$, which were higher in fed status. It could be suggested that in this animal species food could prevent intestinal first pass effect, one of the main effect of tramadol metabolism. This hypothesis is supported by the highest N-desmethyltramadol plasma concentrations found in fasting state.

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