COMPARATIVE PRODUCTION OF THE ACTIVE TRAMADOL METABOLITE O-DESMETHYL-TRAMADOL (M1) IN DOMESTIC ANIMAL SPECIES

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Tramadol is an analgesic drug acting centrally and structurally related to morphine, which interacts with opioid receptors and inhibits the reuptake of noradrenaline and serotonine (1). In veterinary medicine tramadol has been recently authorised for the use in dog, and its efficacy for the management of moderate to severe postoperative pain has been assessed in dogs (2) and other domestic species where the extra label use of commercial preparations is adopted. In man and laboratory animal species, tramadol is metabolized in the liver; one of the main product, the O-desmethyl (M1) metabolite, with about 200 fold higher affinity for the opioid μ receptors than the parent compound is produced by the cytochrome P450 enzyme CYP2D6(3). Aim of this work was the preliminary study of M1 production among cats, dogs and horses, as several indications suggest that it plays a significant role in the analgesic effect of tramadolo also in this domestic animal species.

Tramadol was administered intravenously at the dose of 2 $mg.kg^{-1}$ in dogs (n. 3) undergoing tibial plateau leveling osteotomy and cats (n. 8) subject to castration and at 2.5 $mg.kg^{-1}$ in horses (n. 5) undergoing clinical examinations. Blood samples were collected before treatment, and at regular intervals from five minutes to eight hours after administration. Tramadol and its M1 metabolite, were assayed in serum by HPLC with fluorescence detection (4). To describe drugs kinetic behaviour, a bicompartmental analysis was used for tramadol, while for the M1 metabolite a non-compartmental analysis was performed.

The M1 metabolite attained concentrations much greater than 10 ng/ml, the lowest concentration associated with its therapeutic efficacy in humans (2), immediately after administration and were equal or above this threshold value for the whole period (8 h) in all the species studied. The behaviour of M1 in cats resulted different from what observed in horses and dogs. In cats the early appearance of M1 metabolite supported an intense metabolism of phase 1, while the relatively higher persistence of M1 could be related to the low activity of glucurono-coniugation typical of this species.

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Acknowledgment: The Authors kindly thank Formevet S.p.A.(Milano) for the support provided.