Biopharmaceutics of Metamizole in Healthy Dogs

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Introduction. Metamizole (MT) is an analgesic and antipyretic drug labelled for use in human and veterinary medicine. After administration, MT is rapidly hydrolysed to the active primary metabolite 4-methylaminoantipyrine (MAA) and other minor metabolites. Among secondary metabolites, 4-aminoantipyrine (AA) is also relatively active. MT seems to be a safe drug compared to other non-opioid analgesics, but there is some evidence suggesting that after prolonged administration MT causes damage to the haematopoietic system in humans. For veterinary use, MT is a drug labelled for use in horses, cattle, swine, and dogs. Pharmacovigilance veterinary data have indicated that the incidence of adverse reactions in the target species is very low.

Aim, Materials and Methods. The aim of the study is to compare the pharmacokinetic profiles of MAA and AA after intravenous (IV), intramuscular (IM), oral (PO) and rectal (RC) administrations of MT in healthy dogs. Six adult, female Labradors, clinically healthy, aged 3–6 years, were enrolled in the study. Dogs were randomly assigned to four treatment groups (research randomizer software), using an open, single-dose, four-treatment, four-phase, unpaired, cross-over design. Tested animals received 25 mg/kg of MT. A one-week wash out period took place between the four phases (to ensure complete metabolism and excretion of MAA and AA), the groups were rotated until the crossover study completed. Blood samples were collected at 5, 15, 30, 45 min and 1, 1.5, 2, 4, 6, 8, 10, 24, 36 and 48 hours after administration of MT and later, after sample extraction, were analysed with HPLC-UV method. The pharmacokinetic calculations were performed using WinNonlin v 5.3.1. The curve fit was performed by a non-compartment analysis.

Results. The HPLC method was revalidated using control dog plasma. Briefly, MAA and AA were linear in the range of 100–5000 ng/mL. LOD was 30 ng/mL and LOQ was 50 ng/mL, respectively. No behavioural changes or alterations in health parameters were observed in all groups of animals after treatment.

Except for the initial phase, the IV and IM concentration *vs.* time profiles were similar. On the other hand, also the PO and RC concentration *vs.* time profiles were similar in shape but not in MAA concentration.

The highest concentrations of MAA were found in the IV, then IM, PO and RC group. The concentration of MAA was higher than that of AA in the IV and IM groups. On the contrary, the concentration of AA exceeded that of MAA six hours after MT administration in the PO and RC group. Surprisingly, the average plasma concentration of AA on the PO group was higher (double) than that of AA in the other treatment groups.

Conclusions. This is the first study reporting the pharmacokinetics (PK) of MAA and AA after IV, IM, PO and RC administrations of MT in dogs. The MAA PK profiles were different according to each route of administration, while the AA PK profiles were similar for IV, IM and RC administrations. Although further studies are needed to understand the metabolic pathway of MT as well as its safety profile, the rectal administration seems to be the less performant route of administration for MT in the dog.