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Pharmacokinetic investigations of the marker active metabolite-4-methylamino-antipyrin after intravenous and intramuscular injection of metamizole in healthy sheep

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Highlights

The marker for metamizole (MT) is its metabolite 4-methylaminoantipyrine (MAA).

MAA plasma concentrations were investigated by a HPLC method (limit of quantification 0.1 μg/mL)

The pharmacokinetic profiles of MAA after IM and IV administrations of MT were very similar.

The pharmacokinetic trends in sheep seem to be more similar to those reported in humans rather than in other animal species.

Abstract

Metamizole (MT) is an analgesic and antipyretic drug labelled for use in humans, horses, cattle, swine, and dogs. MT is rapidly hydrolyzed to the primary metabolite 4-methylaminoantipyrine (MAA). MAA is formed in much larger amounts compared to other minor metabolites, and it has been selected from the regulatory European Medicines Agency as a marker residue for MRL calculation. The aim of this research was to evaluate the pharmacokinetic profiles of MAA after 20 mg/kg MT by intravenous (IV) and intramuscular (IM) administrations in healthy sheep. Twelve sheep were randomly allocated to two equal treatment groups according to a 2x2 crossover study. Blood was collected at predetermined times within 36 h and plasma was analysed by a validated HPLC UV method. No behavioural changes or alterations in health parameters were observed in the IV or IM groups of animals during or after (up to 7 days) the drug administration. Plasma concentrations of MAA after IV administration of MT were detectable from 5 min to 8 h in all the sheep, they were still detectable at 10 h in two animals, and the plasma quantification of MAA was possible from 5 min to 10 h in all the animals after IM administration. The only two significantly different parameters between the groups were maximum concentration (C_{max}) and time to maximum concentration (T_{max}) ($P<0.01$). The AUC_{IM}/AUC_{IV} was 1.12. The present study showed that no clinically relevant difference in the MAA was found after IM and IV administration of MT. Further studies are now necessary to assess the safety and efficacy profile of MT in sheep.

Keyword: Analgesic; Small Ruminants; Dipyrone; Metabolism; Pharmacokinetics

1. Introduction

Metamizole (sodium N-[(2,3-dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl)-N-methylamino]methanesulphonate) (MT), also known as dipyrone, is a pyrazolone derivative (Brogden, 1986), introduced to pharmacotherapy in 1922 in Germany (Hinz et al., 2007). This is one of the strongest non-opioid analgesic drugs, used in both human and veterinary medicine for the treatment of pain and fever (Baumgartner et al., 2009). It is a weak COX-1 and COX-2 inhibitor (Botting, 2000) but a strong COX-3 inhibitor (Chandrasekharan et al., 2002). MT is on the human and veterinary market in several countries (European states, Asia, and South America) but has been withdrawn in others (Sweden, USA, Japan, UK, Australia, and Iran) because of safety concerns in humans. Although MT seems to be a relatively safe drug (Bigal et al., 2002; Imagawa et al., 2011) compared to other non-opioid analgesics there is some evidence, which is not unanimously accepted, suggesting that after prolonged administration MT might cause some damage to the haematopoietic system, triggering leukopenia, agranulocytosis and even aplastic anemia in humans (Hedenmalm and Spigset, 2002; Garcıa-Martınez et al., 2003; Basak et al., 2010). However, pharmacovigilance veterinary data have indicated that the incidence of adverse reactions in the target species is very low (Committee for Veterinary Medicinal Products, 2003). For veterinary use, MT is administered parentally in the dose range of 20-50 mg/kg body weight (package leaflet, Biovetalgin, BioWet, Drwalew, Poland).

There is a paucity of data on the pharmacokinetic properties of MT in animals, although the fate of MT administered to humans has already been described (Levy et al., 1995). MT is considered a prodrug which, in a hydrous environment, undergoes spontaneous breakdown to numerous metabolic products (Vlahov et al., 1990; Levy et al., 1995). The parental drug is detectable in blood serum for just a few minutes after intravenous administration, but not after oral dosing. It is also not detectable in urine (Vlahov et al., 1990). In humans, MT is rapidly hydrolyzed to the primary metabolite 4-methylaminoantipyrine (MAA). MAA is further metabolized to 4-

formylaminoantipyrine (FAA), which is an end-metabolite, and to 4-aminoantypyrine (AA) (Levy et al., 1995). AA is acetylated to 4-acetylaminoantipyrine (AAA) (Vlahov et al., 1990; Levy et al., 1995; Rogosch et al., 2012). MAA and AA are active metabolites (Weithmann and Alpermann, 1985; Vlahov et al., 1990). The European Medicines Agency (EMEA) dossier reports that in bovine, porcine, and equid species, MAA has been selected as a marker residue for maximum residue limit (MRL) calculation (Committee for Veterinary Medicinal Products, 2003).

To the best of the Authors' knowledge, no reports are present on the pharmacokinetics of MT and its main metabolite MAA in sheep. Hence, the aim of the present study was to evaluate the pharmacokinetic profiles of MAA after intravenous (IV) and intramuscular (IM) administrations of MT in healthy sheep.

2. Materials and Methods

2.1. Chemicals and reagents

Pure MAA analytical standard (> 99.0% purity) was obtained from Toronto Research Chemicals (Toronto, Canada). The Internal Standard (IS) metoclopramide powder (> 99.0% purity) was supplied by Sigma-Aldrich (St. Louis, MO, USA). Sheep control plasma samples were collected in untreated healthy sheep belonging to the same flock where six animals were selected for the treatments.

2.2. Animal treatment and sampling

Twelve female healthy adult Massese sheep (3-10 years old) of a body mass between 38 and 55 kg were enrolled in the study, which was performed with approval from the Ethical Committee for Animal Experimentation of the University of Camerino. Sheep were kept indoors in a group pen (400 × 400 cm) and fed a commercial pellet and hay diet. On the day of the experiment, twelve sheep were moved into individual stalls where the animals remained in visual contact with each other. The dimensions of each pen were: length 160 cm, width 66 cm and height 110 cm. Pens were

bedded with straw. Sheep were acclimatized to the stalls and handlers prior to commencing the study. Sheep were deprived of food for 8 h prior to the commencement of the experiment while water was available *ad libitum*. Hay and water were available *ad libitum* from 2 h after treatment administration.

Animals were randomly allocated to two treatment groups (A=6 and B=6) according to an open, single-dose, two-treatment and two-period crossover design experiment. Two jugular venous catheters, one in each side (for MT administration and for sample collection, respectively), were placed in each animal 1 day prior to commencement of the study. The group A animals received a single dose of MT (20 mg/kg) by intravenous injection (IV) (Biovetalgin, injectable solution 500 mg/mL, BioWet, Drwalew, Poland) while the group B animals received MT at the same dose by intramuscular injection (IM) (Biovetalgin, injectable solution 500 mg/mL, BioWet, Drwalew, Poland). The dose was selected based on package leaflet recommendations. An interval of 1 week (wash-out period) was observed to ensure complete metabolism and excretion of MAA. After this period the groups were rotated and the crossover study completed. By the end of the study each sheep had received MT by both administration routes. The blood (2 to 3 mL) was collected via previously inserted catheters at assigned times (0, 15, 30, 45 min and 1, 2, 4, 6, 8, 10, 24 and 36 h). The samples were centrifuged at 1,006 x *g* within 30 min of collection and the harvested plasma was frozen immediately and stored at -20° C. Samples were analysed within 1 week of the collection.

2.3. HPLC-FL

The analytical method was based on a previous method (Domínguez-Ramírez et al., 2012) with slight modifications. The HPLC system was an LC Jasco (Como, Italy) that consisted of a quaternary gradient system (PU 2089 PLUS), in line with an ultraviolet detector (Jasco UV-975) set at 254 nm. The chromatographic separation assay was performed with a Luna C18(2) analytical column (250 mm × 4.6 mm inner diameter, 5 μ particle size [Phenomenex, Bologna, Italy]) preceded

by a security guard column with the same stationary phase (C18(2) [Phenomenex, Bologna, Italy]). The system was maintained at 25° C. The mobile phase consisted of acetonitrile:amonium acetate (20 m*M*) solution, pH 5 (20:80, v/v) at a flow rate of 1 mL/min. The elution of the substances was carried out in isocratic mode.

2.4. Sample extraction

The procedure was performed in a 15 mL polypropylene vial. A 0.5 mL aliquot of plasma sample was added to 100 µL of IS (25 µg/mL). After 30 sec vortexing, 0.1 mL sodium hydroxide (1 N) was added and the sample vortexed again. An aliquot of 4 mL of ethylacetate: methylene chloride (3:7, v/v) was added, then vortexed (30 sec), shaken (60 osc/min, 10 min) and centrifuged at 10,956 x *g* (rotor radius 5 cm) for 10 min at 10° C. Three mL of supernatant was collected in a new 15 mL screw cap vial. The organic phase was evaporated under a gentle stream of nitrogen (40° C) and reconstituted with 100 µL of mobile phase. Fifty µL of this solution was injected onto the HPLC.

2.5. Pharmacokinetic analysis and statistical analysis

The pharmacokinetic calculations were carried out using WinNonlin v 5.3.1 (Pharsight Corp). The curve fit was performed by a non-compartmental analysis. The pharmacokinetic parameters are presented as mean ± standard deviation.

In order to make comparisons across treatments, the different parameters were first tested for normal distribution and variance homogeneity. The pharmacokinetic parameters between the groups were compared by a Student's t-test. In all experiments, differences were considered significant if $P < 0.05$.

3. Results

The HPLC method was revalidated using control sheep plasma. Briefly, MAA was linear in the range of 100–2,500 ng/mL. LOD was 30 ng/mL and LOQ was 100 ng/mL, respectively. When samples exceeded the upper limit of the range, they were re-analysed after appropriate dilution. The intra-day repeatability was lower than 4.3%, whereas accuracy was lower than 5.9%. No behavioural changes or alterations in health parameters were observed in the IV or IM groups of animals during or after (up to 7 days) the drug administration.

Plasma concentrations of MAA after IV administration of MT were detectable from 5 min to 8 h in all the sheep and to 10 h in 2 sheep. After IM administration of MT, MAA could be quantified in plasma from 5 min to 10 h in all the animals. MAA plasma concentration was higher in the IV than in IM group at 5 min, while at 15 min, the values became similar. From 30 min to 2 h, MAA plasma concentrations were higher in IM than in IV group, while from 4 to 10 h, the concentration profiles overlapped. The percent of AUC that was extrapolated to infinity ($AUC\%_{Extrap}$) was always <20% in all the subjects. The average pharmacokinetic curves are shown in Figure 1. The main pharmacokinetic parameters are reported in Table 1. The only two significantly different parameters between the groups were T_{max} and C_{max} ($P<0.01$). Although the half-life values in both groups showed no significant difference, the half-life was longer in the IV than in IM group. The AUC_{IM}/AUC_{IV} ratio was 1.12.

4. Discussion

MT is known to possess powerful pain-relieving, antipyretic and spasmolytic properties (Levy et al., 1995) and does not have the contraindications or limitations usually observed with opioids or NSAIDs (Avellaneda et al., 2000; Kemal et al. 2007; Zukowski and Kotfis, 2009; Baumgartner et al., 2009; Edwards et al., 2010). MT has been shown to be a safe and important drug for the management of pain but its use in humans is still controversial. There is plenty of literature attesting to the analgesic efficacy of MT in human beings (Olson et al., 1999; Avellaneda et al., 2000; Kemal et al., 2007; Zukowski and Kotfis, 2009; Edwards et al., 2010; Korkmaz Dilmen

et al., 2010). In veterinary medicine however, the scenario is totally different since the evidence from veterinary studies is not as strong as that from the human literature. There are some data available concerning MT clinical and side effects in horses (Roelvink et al., 1991), rabbits (Baumgartner et al., 2009), rats (Silva-Moreno et al., 2009), and dogs (Imagawa et al., 2011; Flor et al., 2013; Teixeira et al., 2013; Zanuzzo et al., 2015) and some concerning the pharmacokinetic profile of its metabolite MAA in horses (Klaus et al., 1997), rats, and dogs (Christ et al., 1973) however, pharmacokinetic and pharmacodynamic data in sheep are totally lacking.

MT is a drug labelled for humans, horses, cattle, swine, and dogs. Despite not being registered in sheep due to concerns regarding residues in milk, it may prove useful in this animal species. Indeed sheep are widely used as an experimental model for various surgical procedures (Coulter et al., 2009). In spite of this, there is a paucity of data regarding the pharmacokinetics and efficacy of analgesic drugs in this species. There is a clear need to identify analgesic drugs and their doses and dose intervals for use in sheep during invasive experimental procedures.

The pharmacokinetic profiles of MAA after IM and IV administrations of MT were very similar. The significant differences found in C_{max} values were ascribable to the routes of administration of MT. The complete/immediate introduction of MT into the vascular compartment (IV injection) may have generated, in the initial minutes, a more rapid metabolic conversion (increasing the C_{max} of MAA) compared to the IM injection where an absorption phase is expected. Despite the abrupt peak of MAA concentration following IV administration, no adverse effects were shown in the animals. The absorption phase may also be responsible for the delayed T_{max}. The similar AUC values (IV vs. IM) showed that the exposition to the drug over time is similar and the difference in T_{max} is likely to be associated with a negligible clinical effect. The HL reported in this study was shorter than those previously reported in dogs (4-5 h; Liischer, 1993) and horses (4.85 h; Klaus et al., 1997). The reason for this discrepancy might be due to a number of factors such as: differences in animal species, route of administration, presence of pathophysiological conditions, age of the animals, and sensitivity of the analytical method. The HL was longer in IV than in IM

group, although there was not a significant difference between the two treatment groups. According to Klaus et al. (1997), longer HL of MAA have been reported in older as compared to younger people. The crossover design used in the present study should have nullified the age factor. Further investigations with a larger animal sample size are needed to clarify this issue.

The C_{max} of MAA in the horse after intravenous administration was about 4 times higher than that reported in the present study, but the AUC values were of the same order of magnitude (127.7 mg/mL/h vs. 145.9 mg/mL/h in horses and sheep, respectively).

5. Conclusion

The MAA pharmacokinetic profiles were similar. Although further studies are needed to understand the metabolic pathway of MT as well as its safety and efficacy profiles in sheep, this study can be the first stone to pave the road for the use of MT in small ruminants.

Conflict of interest statement

None of the authors has any financial or personal relationships that could inappropriately influence or bias the content of the paper.

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Figures' captions

Fig. 1. Mean plasma concentrations of 4-methylaminoantipyrine (MAA) vs. time curves following intravenous (--○--) and intramuscular (—●—) administrations of 20 mg⁄kg metamizole (MT) in healthy sheep (*n* = 12). Bars represent the standard deviations. ¥ Data recorded in 2 animals in the intravenous group.

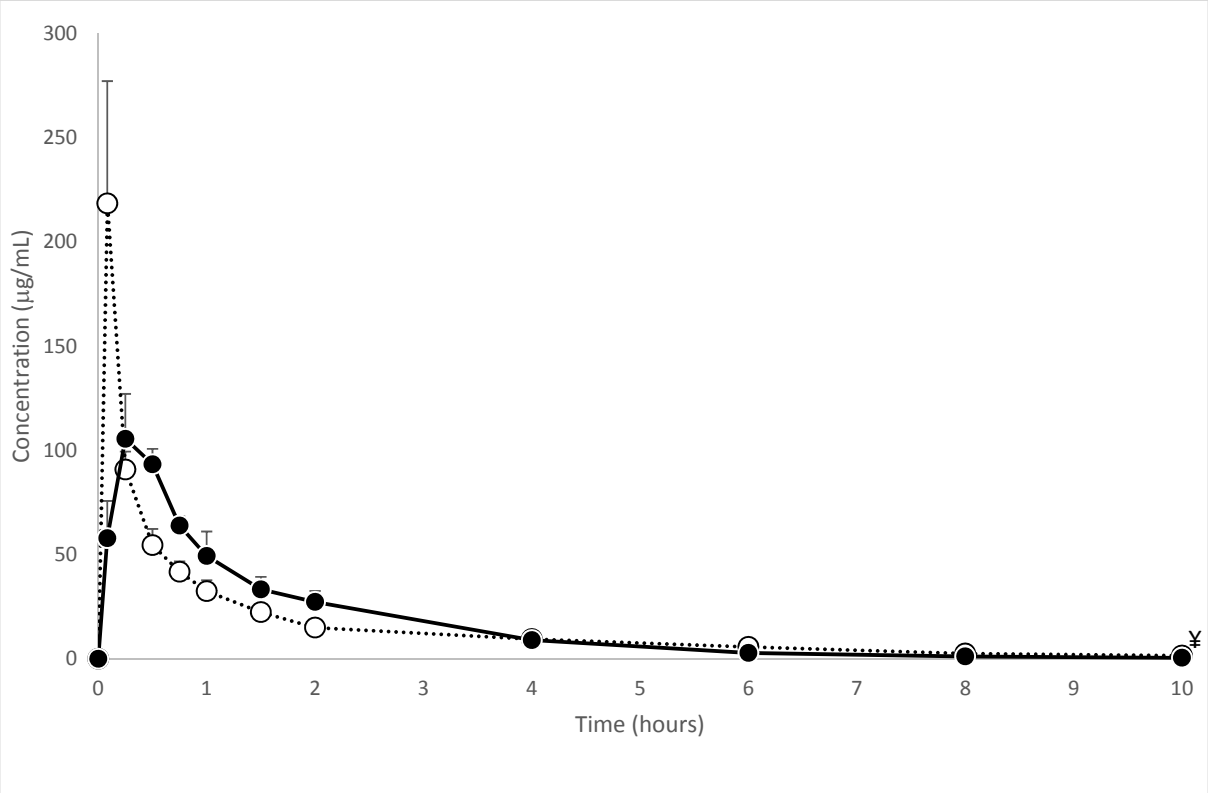

Table 1 Main pharmacokinetics parameters of 4-methylaminoantipyrine (MAA) following single intravenous (IV) and intramuscular (IM) administrations of metamizole (MT) (20 mg/kg) in healthy sheep (n=12).

		IV			IM	
Parameter	Mean		SD	Mean		SD
R^2	0.99	±	0.01	0.99	±	0.02
λz (1/h)	0.24	±	0.05	0.48	±	0.04
$t_{1/2}$ λz (h)	3.01	±	0.52	1.45	±	0.13
T_{max} (h)*	0.08	±	0.00	0.29	±	0.10
C_{max} (µg/mL)*	218.46	±	58.69	108.24	±	16.32
AUC $_{0\text{-last}}$ (h µg/mL)	145.91	±	15.48	163.93	±	24.87
AUC $_{0\text{-}\infty}$ (h µg/mL)	161.42	±	21.25	165.04	±	24.63
AUMC $_{0\text{-}\infty}$ (h^2 µg/mL)	457.90	±	106.24	282.44	±	42.64
MRT (h)	2.81	±	0.34	1.71	±	0.07

R^2 = correlation coefficient; λz = terminal phase rate constant; $t_{1/2}$λz = terminal half-life; T_{max} = time of peak; C_{max} = peak plasma concentration; $AUC_{0\text{-last}}$= area under the plasma concentration-time curve; $AUC_{0\text{-¥}}$= area under the plasma concentration-time curve extrapolated to infinity; $AUMC_{0\text{-¥}}$= area under the first moment curve from zero to infinity; MRT = mean resident time; SD = standard deviation.

* Statistically different value between the treatment groups.