Pharmacokinetics of marbofloxacin, after one bolus oral administration in buffaloes calves: Preliminary study.

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ABSTRACT: Buffalo breeding system has a great economic importance in South-America, principally in marginal or sub-tropical lands. The therapeutic recommendations applied to a single ruminant species are extrapolated to others but important differences among those were recognized. Marbofloxacin bolus is indicated in the treatment of neonatal gastroenteritis caused by *Escherichia coli*, in calves (25-50kg). The aim of this study was determined the pharmacokinetic behaviour of marbofloxacin after oral administration, as bolus, following the label approved recommendations to cattle. One bolus (50 mg) was administered in two clinically healthy buffaloes (two days-old, 48-50kg). Plasma concentrations of the marbofloxacin were determined by a HPLC/u.v. method. After oral administration, the values obtained were: tmax=0.5-6h, Cmax= 1.19-0.04µg/mL, AUCt=1.57-0.38µg·h/mL and MRTt= 3.34-6.92h, for calves 1 and 2 respectively. Fluoroquinolones act by concentration dependant killing mechanism, so high plasma concentration initially is important. For this reason, the recommended dose of 1mg/kg is inadequate in buffaloes.

Key words: Fluoroquinolone, Marbofloxacin, Buffalo, Pharmacokinetic, Oral bolus.

INTRODUCTION - Buffalo breeding system have a great economic importance in South America, principally in marginal or sub-tropical lands. Likewise, beef cattle is raised together with buffalo in some areas, consequently, similar diseases may affect both species. In this case the implementation of the same therapy is a common situation. In spite of these facts, there are no studies comparing the pharmacokinetics between buffalo and holstein calves in similar conditions of age/weight, drug or dose. Marbofloxacin is a synthetic, bactericidal, antimicrobial, belonging to the fluoroquinolone group which acts by inhibition of DNA gyrase. It has a broad-spectrum activity in vitro against mycoplasma, Gram-positive and Gram-negative bacterias. Strains with MIC ≤ 1 µg/ml are sensitive to marbofloxacin whereas strains with MIC ≥ 4 µg/ml are resistant to marbofloxacin. This fluoroquinolones is indicated for treatment of gastroenteritis and mastitis caused by sensitive strains of *Escherichia coli* in neonatal calves and dairy cows, respectively (Schneider *et al.,* 2004).
Oral bioavailability approached 100% in several species (EMEA 1996). In the past, the therapeutic recommendations applied to a single ruminant species were extrapolated to

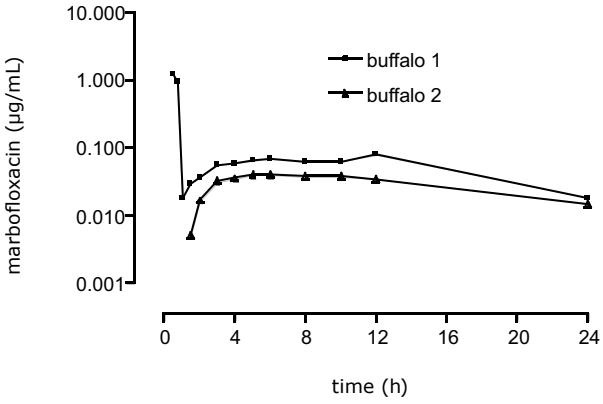
the others because no important differences among cattle, sheep, goats and buffaloes were recognized. However, a different pharmacokinetic behavior of antimicrobials has been described along the ruminant species (Elsheikh *et al.,* 1997). Physiological differences between buffaloes and others ruminant (such as corporal composition, percentage of adipose tissue, reproductive cycle, hepatic metabolism or renal excretion) have been described (Groves, 1989, Waxman *et al.,* 2001). For the above mentioned reasons, the aim of this study was determined the pharmacokinetic behaviour of marbofloxacin after oral administration, as bolus, following the label approved recommendations to cattle.

MATERIAL AND METHODS - ***Animals and experimental design.*** The experiment was performed in two male buffaloes two days old and weighing 48 and 50 kg.
The animals received one bolus of marbofloxacin equivalent to a dose of 1 mg/kg b.w. (Marbocyl bolus®, Vétoquinol, Lure, France). Blood samples were collected through a catheter placed in the left jugular vein, at 10, 20, 30, 45 min, and 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 24, h after administration. The samples were centrifuged at 1800 g for 20 min within 30 min after collection. Plasma aliquots were frozen (-80ºC) until assayed.
Analytical assay. The plasma marbofloxacin concentrations were determined by high performance liquid chromatography (HPLC) modified from a previously published method (Schneider *et al.*, 1996). Marbofloxacin was provided by Vétoquinol, Lure, France and ofloxacin was used as internal standard (Sigma Chemical CO., St. Louis, MO, USA). The UV detection wavelength was 295 nm and the flow rate was 1 ml/min. The quantification limit was 0.025 µg/ml and the method was linear between 0.025 µg/ml and 15 µg/ml. The inter-assay and intra-assay reproducibility were below 10% (coefficient of variation).
A volume of 300 µl of plasma was placed into 15 ml screw-capped tubes. 75 microliters of the internal standard solution (ofloxacin, 5 µg/ml in formic acid 0.1 N) and 4,5 ml of trichloromethane were added. After being agitated during 10 min in a horizontal agitator, the samples were centrifuged at 3200 g for 7 min and the organic layer transferred to another tube from where it was evaporated under nitrogen stream at 40 ºC. The samples were redisolved in 150 µl of mobile phase and a 50 µl aliquot was injected into the HPLC system.
Pharmacokinetic analysis. Plasma levels of marbofloxacin were subjected to model independent analysis, statistical moments were used to compute the non compartmental with the help of PCnonlin® V 4.0 software package. The observed Cmax and tmax were used. Area under curve (AUC) and mean residence time (MRT) from time 0 to last time were calculated for each animal.

RESULTS AND CONCLUSIONS - After oral administration, marbofloxacin reached a low plasma concentrations and a high variability was observed between both animals. A peak of 1.19-0.04µg/mL was obtained to 0.5-6h, for calves 1 and 2 respectively. A low values of AUC (1.57-0.38µg·h/mL) and a relative short permanence (3.34-6.92h) were observed in this study. Although there are no published data concerning antibacterial activity of marbofloxacin against buffaloes isolates, previous studies showed the bactericidal activity of marbofloxacin against bovine pathogens (Meunier *et al*., 2004). Based on the available published reports on the value of surrogate markers to predict clinical success, a C_{max} / MIC ratio of 10 or an AUC/MIC ratio of 125-250, have been associated with optimum bactericidal effect. High C_{max} / MIC ratios also have been associated with a lower incidence of resistance development (Walker, 2000).

Using the MIC breakpoint of 0.1 and 0.16 μg/mL, the pharmacokinetic parameters determined in our study and the pharmacodynamic variables correlated to outcome of infection the optimal dosage regimen could be estimated. A single oral marbofloxacin bolus (1 mg/kg) dose gave a Cmax/MIC of 74-2.5 and 11.9-0.40 and AUC/MIC of 98-24 and 15.7-3.8 h values for MIC values of 0.016 and 0.1 μg/mL, respectively. However, the targeted Cmax/MIC and AUC/MIC ratios suggested have been based on *in vitro* and *in vivo* studies performed with inmunosupressed laboratory animals or on clinical studies involving humans with serious illness (Shojaee Aliabadi, F. and Lees, P., 2002). The results obtained indicated that there is a high variability and the recommended dose of 1mg/kg is inadequate in buffaloes. If a higher dose of 2 mg/kg is recommended in carnivorous species, in pre-ruminant animals a minimal dosage of two bolus/animals (≈2 mg/kg) should be studied.

Figure 1. Marbofloxacin plasma concentration vs. time curves obtained after the recommended oral administration (one bolus: 1 mg/kg) in buffaloes.



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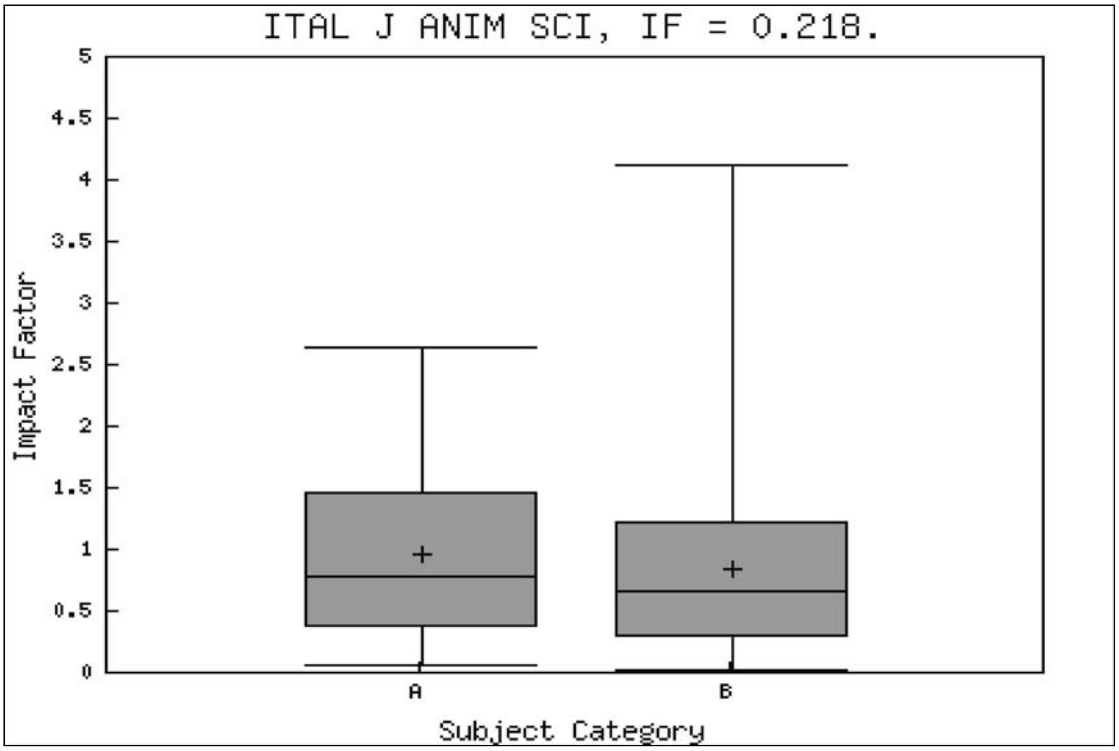

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