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Research Article

Effects of Mastitis on Pharmacokinetics of Elimination with Milk of BenzimidazoleAnthelmintics

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Abstract: The current study was performed to determine the effects of mastitis on behaviour of benzimidazole anthelmintic drugs in milk. Seven Brown Swiss cows with subclinical mastitis infection in one or two udder quarters and not in the first trimester period of pregnancy were used in this study. The study was conducted in cross-over design method. Albendazole (ABZ), triclabendazole (TCBZ) and fenbendazole (FBZ) at 7. 5 mg/kg, 10 mg/kg and 7.5 mg/kg single oral doses were applied to animals with mastitis and after mastitis treatment respectively. The milk and blood samples were collected at prior to drug administration and following drug application zeroth, 8^{th}, 16^{th}, 24^{th}, 36^{th}, 48^{th}, 72^{nd} and 120^{th} hours. The milk and blood samples were extracted with SPE (Solid Phase Extraction) and analysed by HPLC. Mastitis caused only the change in the behaviour of ABZ in milk. AUC_{milk}/AUC_{plasma} rates were calculated respectively as 0.96, 0.95, 0.97, 0.92, 0.91 and 0.89 for albendazolesulfoxide (ABZSO), albendazolesulfon (ABZSO2), triclabendazolesulfoxide (TCBZSO), triclabendazolesulfon (TKBZSO2), fenbendazole (FBZ) and fenbendazolesulfoxide (FBZSO) in animals without mastitis. These rates in animals with mastitis were 1.28, 1.21, 0.98, 0.93, 0.97 and 0.94 respectively. While the biological half-life of ABZSO and ABZSO2 were found as 24.01 and 20.92 hour in milk of animals with mastitis, these parameters were 17.49 and 19.77 hour in milk of animals without mastitis. The biological half-life of plasma for ABZSO, ABZSO2, TKBZSO, TKBZSO2, FBZ and FBSO were calculated as 10.55, 9.94, 24.11, 31.75, 14.68, 20.13 and 16.75 hours in healthy animals. Inflammatory diseases such as mastitis may change pharmacokinetic behaviour of some drugs in the milk.

Keywords: Benzimidazoleanthelmintics, mastitis, pharmacokinetic

INTRODUCTION

Pharmacokinetic parameters and withdrawal times of veterinary drugs have been determined in healthy animals at standardized test conditions (Paige *et al*., 1997; MacNeil, 2005; Serratosa *et al*., 2006). The disease with inflammation cause the change physiological processes leads to change the pharmacokinetics of drugs.

Some of these changes are the increase in vascular permeability and plasma protein ratio and changes in biological fluids pH, transmembrane protein activity, the activity of drug metabolizing enzyme, gastrointestinal organs movements and tissues blood perfusion (Blood *et al*., 1983; Gips and Soback, 1999; Gruet *et al*., 2001; Gehring and Smith, 2006). The milk is an important drug excretion way in lactation animals. Mastitis affects the functions of the mammary gland, milk composition, pH and drug excretion with milk.

Anthelmintic are the second the most widely used drug group in livestock. Benzimidazoles are anthelmintic drugs is a group of commonly used in ruminants for the treatment and prevention of infections caused by *Giardia*, nematodes, cestodes and trematodeshelminthes.

Benzimidazoles are absorbed from digestive tract poorly, because they are low water soluble. Benzimidazoles are metabolised to sulfon and sulfoxide metabolites and sulfoxide metabolites irreversible convert to sulfon form. Their sulfoxide metabolites are pharmacologically active. Albendazole, triclabendazole and fenbendazole as the parent compounds are found only in the digestive tract while their metabolites are found different in tissues and biological fluids. No study related to impact of mastitis on milk excretion of benzimidazoles in literatures has been reached. Therefore, the objective of this study was to investigate the pharmacokinetic profile of benzimidazole

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anthelmintics in lactating dairy cows with subclinical mastitis. In addition, blood pharmacokinetics parameters of albendazole, triclabendazole and fenbendazole were also calculated in healthy animals.

MATERIALS AND METHODS

Animal trials: The study was carried out seven Brown Swiss cow with mastitis in one or two udder quarters and not in the first trimeter of pregnancy in a private commercial dairy farm (Kartal, Istanbul). The mastitis was diagnosed by California Mastitis Test (CMT). The study was used cross-over design method.

In the first phase of the study, albendazole (Vetalben Fort oral tablet, 1200 mg Albendazole, VETAS), triclabendazole (Levatrizol oral tablet, 375 mg Levamizole and 600 mg Triclabendazol, VETAS) and fenbendazole (safe-guard, Fenbendazole 92 g paste %10, Intervet) 7. 5 mg/kg, 10 mg/kg and 7.5 mg/kg doses at single doses were administered by orally to cows with mastitis, respectively. To avoid drug interaction, any systemic drug administration were not made to animals and also mastitis treatments were performed by local (intramammary) application of antibacterial (Masticol LC intramammary suspension, 200 mg Ampisilin sodium and 200 mg Diclocsasilin sodium, Vilsan) drugs. Prio to drug administration and following drug application at 8^{th}, 16^{th}, 24^{th}, 36^{th}, 48th, 72^{nd} and 120^{th} h milk from mastitic mammary glands and blood samples from the jugular vein were collected. The collected samples were stored at freezer until they were analyzed. Milk of animals not intended for human consumption for 10 days.

The second phase of the study, the same study protocols were applied to animals after mastitis treatment. Treatment effectiveness was checked by CMT (the 20^{th} day of trial).

The study was conducted according to guidelines of The Ethics Committee of the Veterinary Control Institute, Pendik, Istanbul,Turkey.

Method: A complete validation of analytical process for the extraction and quantification of benzimidazole was certified before the analysis of milk and blood samples.

The methods used in this study were Berlin BgVV -BVL` s reference method which is the European Union reference laboratory (Community Reference Labarotory-CRL).

Milk Extraction: 5 ml of milk samples were taken placed in 50 ml centrifuge tubes and added 2.5 g of anhydrous sodium sulphate and 10 ml of acetonitrile then wortexed one minute. Also 10 mL of ethyl acetate was added and one minute by vortexing. Tubes were centrifuged at 3000 RPM for 10 minutes at 4°C. Supernatant was transferred to another tube. Repeated extraction with 10 ml of ethyl acetate and the combined upper phases were dried at 60°C under N2. Dried extract was dissolved in 1 ml of $K_2H_2PO_4$ and 5 ml of 0.1 M $NaHCO_3$.Analyte was transferred into conditioned SPE (C18) cartridges. Cartridges was eluted 4 ml of ethyl acetate:acetonitrile and elute dried under N_2. Dried elute was dissolved in 200 µl of mobile phase and then transferred to HPLC vials.

Blood extraction: 1.5 mL of heparinised blood samples were placed in 10 ml test tubes and added 100 mM sodium carbonate solution then wortexed. Analyte was transferred into conditioned SPE (C18) cartridges. Cartridges was eluted 4 mL 0f ethyl acetate:acetonitrile and elute dried under N_2. Dried elute was dissolved in 200 µl of mobile phase and then transferred to HPLC vials (BGVV, 2002).

Analysis for drugs: Experimental and fortified blood and milk samples were analysed for drugs by HPLC. The analytical procedure was performed by adapting the method which has been developed and validated for residue surveillance of tissues. 20 µl of each sample were injected in a Thermo Finnigan MSQ LC-MS (Italy) system with two LC- solvent pumps (Thermo Finnigan Surveyor LC Pump, Italy), an automatic sample injector (Thermo Finnigan Surveyor Autosampler, Italy), an UV detector (Thermo Finnigan Surveyor PDA detector, Italy). Data and chromatograms were collected and analysing using the software (Xcalibur 1.4. SR1 DSQ 1.4.1., Italy). A Synergi C18 (5 µm, 250×4.60 mm) reversed-phase column (Phenomenex, CA, USA) was used for separation. Elution from the stationary phase was carried out a flow rate of 0.8 ml min. using acetonitrile/methanol (70/30) and 0.01 M ammonium formate buffer as the mobile phase. The gradient changed linearly from 90:10 (acetonitrile/methanol and ammonium formate) to 60:40 in 30 min, the maintained for 35/65 in 15 min and modified to 90:10 65.min. The detection of drugs/metabolites was done at a wavelength of 254, 290 and 298 nm. The limit of quantitation was 0,01 µg/L and standard curve was linear within the range from 0.01 to 50 mg/L (r^2 = 0.998). The recoveries from blood and milk samples were more than %80.

Pharmacokinetic and statistical analyses of the data: The pharmacokinetic analyses of plasma and milk concentration time data was carried out applying a noncompartmental model using the WinNonlin (Version 4.1., Pharsight Corporation, North Carolina, USA) computer program. Pharmacokinetic parameters for each animal were analysed using non-compartmental model analysis with extravascular input. The maximum plasma concentration (C_{max})and time to reach maximum concentration (t_{max}) were obtainedfrom the plotted concentration-time curve of each drug

in each animal. Analysis of variance (ANOVA) was performed to assess period, treatment and crossover affects.

RESULTS AND DISCUSSION

Pharmacokinetic parameters of albendazole, triclabendazole and fenbendazole expressed as mean ±SD are presented in Table 1.

The majority of chemotherapeutic drugs by passive diffusion through the blood-milk barrier accumulated of various concentrations in milk. Mammary gland, the pH of 6.5-6.8 and is an important organ for excretion of basic drugs (Gruet *et al*., 2001; Ito and Lee, 2003; Holford, 2004). The literature indicates that inflammatory mammary glands associated acute mastitis cases, the blood-milk barrier more permeable and changing the physicochemical properties of milk result in considerable alter pharmacokinetics of antimicrobial drugs and can also affect drug excretion to milk. Many the hosts, the drug and the environmental linked factors modify pharmacokinetic behaviour of the drug (Gips and Soback, 1999; Rantala*et al*., 2002; Schneider *et al*., 2004; Sérieys *et al*., 2005; Kietzmann *et al*., 2008; Lucas *et al*., 2009) (Table 2).

Albendazole and triclabendazole as parent compound could not be detected in the blood and also FenbendazoleSulfoxide (FBZSO) in the milk as mentioned in literatures.

In the present study, it has been determined that mastitis only changes the behaviours of albendazole metabolites in milk but not fenbendazole and triclabendazole. Similar values observed for peak concentration ($C_{max,}t_{max}$,absorbtion and distribution rate constants ($t_{1/2\beta}$,MRT_{last}). However, Table 3 shows higher $AUC_{milk\ 0\text{-}24}$ and $AUC_{milk\ 0\text{-}72}$ were obtained for albendazole than for fenbendazole and triclabendazole. Both ABZSO and ABZSO2's AUC_{milk}, the milk biological half-life and the milk/plasma ratios in the cows with mastitis were statistically than the healthy cows ($p<0.05$, Table 3 and 4). But no difference observed between fenbendazole and triclabendazoleAUC_{milk}, the milk biological half-life and the milk/plasma ratios in the cows with mastitis.

Albendazole behaviour change in the milk of cows may be related to its physicochemical properties. Another factor that of which are effective solute transport from plasma to the milk BCRP (Breast Cancer Resistance Protein) transmembrane protein may play a role. Albendazole is a substrate of BCRP and that `s carrier protein activity changed in the inflammatory events that have been reported (Merino *et al*., 2005; Muenster *et al*., 2008; Poller *et al*., 2010). We found that mastitis caused more change behaviour of ABZSO and ABZSO2. This difference may be associated to different physicochemical property of metabolites. Physicochemical properties of each drug and its metabolites in benzimidazole class are different.

The half-life of triclabendazole metabolites are longer from than the half-life of albendazole and fenbendazole. Reasons of this may be plasma protein binding rate and distribution volume of triclabendazole. The plasma protein binding rate of triclabendazole metabolites are high. On the other hand, stated on the contrary; we found large volume of distribution of triclabendazole metabolites (Table 1 and 2). We think that the calculated volumes of distribution forbenzimidazoles are not healthy data. Because, rumen serves as a physiological reservoir for benzimidazoles.Also benzimidazoles are irregularly absorbed from gastrointestinal tract and there is a cycle between the
circulatory system and the digestive tracts for benzimidazoles (Lanusse *et al*., 1995; Capece *et al*., 2001; Mestorino *et al*., 2008).

Table 1: Pharmacokinetics parameters of triclabendazole, albendazole and fenbendazole determined after oral administration at a dose rate 10 mg/kg and 7.5 mg/kg in healthy cows

Pharmacokinetic parameters	ABZSO	ABZSO2	TCBZSO	TCBZSO2	FBZ	FBZSO	FBZSO2
T_{max} (h)	13.95±1.81	21.40±3.88	23.90±2.1	45.10±6.95	27.72± 2.93	37.11±4.40	45.02±1.43
C_{max}(µg/ml)	3.5±0.76	3.2±1.73	14.55±2.66	12.22±2.33	0.46±0.08	0.12±0.01	0.52±0.08
AUC_{last}(µgh/ml)	66±14	55±25	660.02±140.4	949.3± 225.3	5.81±0.12	1.58±0.09	6.13±0.14
$t_{1/2ab}$ (h)	4.67±1.02	6.37± 1.13	6.85± 1.22	9.27± 1.31	5.25± 0.89	7.28± 0.93	10.8± 1.47
$\alpha(h^{-1})$	0.53± 0.11	0.52± 0.11	0.81± 0.13	0.83± 0.14	0.18±0.06	0.12±0.03	0.23± 0.27
$\beta(h^{-1})$	0.05± 0.009	0.05± 0.009	0.008± 0.001	0.007± 0.001	0.014± 0.002	0.010± 0.001	0.015± 0.03
$t_{1/2\alpha}$ (h)	1.24± 0.12	1.18± 0.11	3.36± 0.25	5.95± 0.39	1.71± 0.16	1.64± 0.15	1.89± 0.17
$t_{1/2\beta}$(h)	10.55± 0.80	9.94±0.85	24.11±1.99	31.75±2.15	12.18±1.44	15.83±1.70	14.19± 1.49
Vd (L)	59± 1.41	61± 1.42	766.1± 50.1	1070.2± 59.9	1.34±0.14	0.89±0.10	1.95± 0.19
$k_{12}(h^{-1})$	0.80± 0.11	0.79± 0.10	2.83± 0.44	2.95± 0.45	0.05±0.09	0.02±0.09	0.07± 0.09
$k_{21}(h^{-1})$	0.35± 0.08	0.37± 0.08	0.91± 0.02	0.93± 0.02	0.05± 0.01	0.02± 0.01	0.06± 0.01

Table 2: Milk pharmacokinetics parameters of triclabendazole, albendazole and fenbendazole determined after oral administration at a dose rate 10 mg/kg and 7.5 mg/kg in healthy cows

Pharmacokinetic parameters	ABZSO	ABZSO2	TCBZSO	TCBZSO2	FBZ	FBZSO2
T_{max} (h)	25.02±1.88	15.99± 1.39	14.85± 1.22	13.19± 1.38	20.19± 1.78	23.64±1.82
C_{max}(µg/ml)	0.922±0.08	0.812±0.06	0.930±0.08	0.873± 0.08	0.120± 0.03	0.166± 0.031
AUC_{last}(µg h/ml)	73.22±6.09	69.18±4.52	728±144.52	902.8± 154.1	6.51± 0.13	8.88± 0.15
$t_{1/2\beta}$(h)	17.49± 0.44*	20.03± 0.46*	17.39± 0.41	15.26± 0.41	30.66±1.22	37.11± 1.93

*: As it is important that as a statistical values are in row ($p<0.05$)

Table 3: Comparison milk pharmacokinetic parameters of triclabendazole, albendazole and fenbendazole determined after oral administration at a dose rate 10 mg/kg and 7.5 mg/kg in mastitic cows

Pharmacokinetic parameters	MASTITIS					
	ABZSO	ABZSO2	TKBZSO	TKBZSO2	FBZ	FBZSO2
c_{max}(µg/mL)	1.122±0.107	0.911±0.086	0.921±0.076	0.868±0.078	0.122±0.031	0.168±0.031
t_{max} (saat)	24.13±1.75	14.58± 1.30	14.21± 1.18	13.00± 1.33	20.25±1.80	24.06±1.85
$t_{1/2\beta}$(h)	24.01± 0.62*	20.92± 0.49*	15.88± 0.38	14.93± 0.39	30.13±1.21	37.49±1.94
MRT_{last} (h)	69.28± 3.54	75.02± 3.93	218.77±8.82	227.30±9.21	135.23± 7.92	129.25± 7.71
$AUC_{milk\ 0\text{-}24}$(µg h/mL)	76.09±6.99*	71.17±6.26*	1195.44 ±82.31	1096.33±175.50	0.619±0.007	0.679±0.009
$AUC_{milk\ 0\text{-}72}$(µg h/mL)	99.46±9.18**	93.95±8.44*	1473.52 ±85.44	1422.30±178.16	0.6795±0.010	0.713±0.011
AUC_{milkt} (µg h/mL)	135.40±11.12**	118.65±10.07**	1933.77±205.50	1875.46±202.40	1.1486± 0.40	1.1722±0.040
AUC_{milk}/ AUC_{plasma}[1]	1.28*	1.21*	0.98	0.93	0.97	0.94

1: $AUC_{milk\ 0\text{-}72}$ (µg h/mL)/ $AUC_{plasma\ 0\text{-}72}$ (µg h/mL) ratio; *:As it is important that as a statistical values are in column ($p<0.05$). **: as it is important as statistical values in row ($p< 0.01$)

Table 4: Comparison milk pharmacokinetic parameters of triclabendazole, albendazole and fenbendazole determined after oral administration at a dose rate 10 mg/kg and 7.5 mg/kg in healthy cows

Pharmacokinetic parameters	HEALTHY					
	ABZSO	ABZSO2	TKBZSO	TKBZSO2	FBZ	FBZSO2
c_{max}(µg/mL)	0.922±0.088	0.812±0.064	0.930±0.081	0.873±0.080	0.120±0.030	0.166±0.031
t_{max} (saat)	25.02±1.88	15.99±1.39	14.85±1.22	13.19±1.38	20.09±1.78	23.64±1.82
$t_{1/2\beta}$ (h)	17.49±0.44	19.77±0.46	17.39±0.41	15.26±0.41	30.66±1.22	37.11±1.93
MRT_{last} (h)	68.55±3.25	73.40±3.80	219.48±8.85	227.93±9.22	138.19± 8.05	130.20± 7.88
$AUC_{milk\ 0\text{-}24}$ (µg h/ml)	66.15±5.88	63.95±5.76	1100.61±172.0	1070.14±170.2	0.615±0.007	0.670±0.008
$AUC_{milk\ 0\text{-}72}$ (µg h/ml)	88.10±7.44	85.21±7.22	1494.86±188.3	1430.30±182.0	0.6825±0.011	0.720±0.012
$AUC_{milktotal}$ (µg h/ml)	119.24±9.05	108.20±8.90	1949.33±208.7	1881.39±204.6	1.1560± 0.41	1.1734±0.042
AUC_{milk}/AUC_{plasma}[1]	0.96	0.95	0.97	0.92	0.91	0.89

1: $AUC_{milk\ 0\text{-}72}$ (µg h/ml)/$AUC_{plasma\ 0\text{-}72}$ (µg h/mL) ratio

Following intraruminal administration at the same dose of albendazole in cattle, the plasma half life of sulphide and sulfone metabolites were found in respectively 9.10 and 8.93 hours (Sanyal, 1997). It can be indicated that this data agree with our findings (10.55 and 9.94). Small difference between our and his data may be associated with administration route and pharmaceutical form differences. Because the residence time of liquid and solid drug form in the rumen are unlike.

The plasma half-life of TCBZSO2 and TCBZSO in 8-9 month calves was determined to be 31.47 and 45.59 hours, respectively (Sanyal and Gupta, 1998). These data are longer than our results. Reasons of this may be dose used by researchers (12 mg/kg), the age and breed difference of animals and feeding protocols. It has been determined that pharmacokinetic profiles of both TCBZSO and TCBZSO were affected by different diets feeding in goats (Gökbulut *et al*., 2007).

The biological half-life of FBZ, OFBZ and FBZSO2 were found to be 7.11, 8.91 and 6.89 hours after intraruminal administration in male calves (Knox and Steel, 1997). Reasons of different between these dates and our results may be associated with difference in animal breed and age, pharmaceutical form and feeding protocol.

CONCLUSION

The passing rate of fenbendazole in healthy animals to the milk lower than the others. Mastitis did not affect the pharmacokinetic behaviour of fenbendazole and triclabendazole in milk. Whereas, caused an increase the half-life and in the rate of excretion to the milk of albendazole. As results, it can be expressed that inflammatory diseases such as mastitis may change pharmacokinetic behaviour of some drugs in the milk. Mastitis is caused significant changes in the behaviour of albendazole in milk, as subclinical mastitis cases suggest that great care should be taken in defining the legal withdrawal period in lactating cows.

Conflict of interest: The authors have no conflicts of interest to declare. None of the authors of this manuscript has a financial or personal relationship with other people that could inappropriately influence or bias the content of the manuscript.

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