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Residues of Sulphadimidine and its Metabolite N_4-acetyl in Camel Milk

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Abstract: Intravenous administration of sulphadimidine (SDM) at a dose of 50 mg kg^{-1} body weight as a single-dose or repeated-dose treatments to lactating camels resulted in residues of SDM and its metabolite N_4-acetyl in milk. Milking twice daily resulted in depletion of SDM and N_4-acetyl residue during a withdrawal period of 5 days after the last injection of the drug. Milk protein binding and concentration of metabolite was very low suggesting that monitoring of sulphonamide residues in milk could be limited to SDM alone.

Key words: Camel, sulphadimidine, residues, milk

INTRODUCTION

The antibacterial treatment of mastitis in lactating animals is of considerable regulatory concern because of the possibility of antibacterial residues in milk[1]. Although intramammary (i.m.m) infusion has been recognized as the route of choice for treating mastitis[2], other investigators have recommended the use of combination of routes for administration of antibacterial agents[1,3]. Over 16% of milk samples collected 96 h post-treatment were positive for antibiotic[3].

Sulphadimidine (SDM) is one of the most extensively used drugs in veterinary medicine for prophylaxis and therapeutics[4]. In camels, SDM is eliminated slowly from the body and the main SDM metabolite detected in plasma is N_4-acetyl derivative (N_4-acetyl)[4,5]. The withdrawal period for SDM and its metabolite is not prescribed in milk of lactating camel, therefore the objective of the present study were to determine the concentration of SDM and its metabolite in milk after administration as a single or repeated-dose treatments and follow the depletion of SDM in milk until its concentration dropped below the maximum residue limit.

MATERIALS AND METHODS

Animals and treatments: Eight lactating one-humped camels, 4-5 years old, weighing 200-250 kg and representing various levels of milk production were used. Animals had free access to hay and water *ad libitum*. The camels were individually milked twice daily at 12 h interval. Sulphadimidine (33.3%, Bremer Pharma GmbH, Germany) as a single dose treatment of 50 mg kg^{-1} (Group 1, 4 animals) or repeated dose treatments of 50 mg kg^{-1} (Group 2, 4 animals) was given intravenously (IV) to animals. The repeated doses were administered daily after morning milking for 3 days.

Collection of plasma and milk samples: Milk samples were collected at every milking from each cow. The first milk samples was taken before injection of drug. Samples were stored in labeled plastic containers at -20°C until analysis. Blood samples were collected from Group 1 and 2 animals into heparinized tubes, centrifuged at 2000 × g and plasma was separated and stored at -20°C until analysis.

Sulphadimidine and its metabolite measurement: The HPLC analysis of SDM and N_4-acetyl was previously described[5]. The mobile phase consisted of methanol, acetonitrile, 0.02 M Sodium acetate, 0.2 M acetic acid and distilled water 15: 4: 27: 50: 3.6, respectively. The detection limit for SDM and N_4-acetyl was 0.1 μg mL^{-1}.

Protein binding: Ultrafilterate of selected plasma and milk samples were obtained with the reusable Micropartition System (Amicon Corp, Leyington, MA). The ultrafilterates obtained were measured by HPLC and percentage protein-binding was calculated as described previously[6]. Values were compared using Student's t-test[7]. The probability value $p<0.05$ was considered significant.

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RESULTS

Sulphadimidine or its metabolite was not detected in any milk samples collected before dosing in single (Group 1) and repeated dose (Group 2) treatments. The mean concentration of SDM and N_4-acetyl in milk was detected at the first milking (12 h) post dosing in both groups (Table 1). Repeated injection of sulphadimidine in Group 2 increased ($p<0.01$) the concentration of both SDM and N_4-acetyl in milk compared to Group 1.

Depletion of SDM and N_4-acetyl to <0.1 μg mL^{-1} occurred at 10th (120 h) and 4th (48 h) milking, respectively, in single-dose treatment. Depletion of SDM and N_4-acetyl to <0.1 μg mL^{-1} occurred at 16th (192 h) and 11th (121 h) milking, respectively, in repeated-dose treatment. SDM concentration were <0.1 μg mL^{-1} at 120 h after the last dose of treatment in both group.

Sulphadimidine and N_4-acetyl plasma protein binding was significantly ($p<0.01$) in single dose treatment (Table 2) higher than in repeated does treatment. The binding of SDM and N_4-acetyl in milk protein was significantly ($p<0.01$) lower than in plasma proteins, the ratio being <1.

Table 1: Mean±SD concentration (μg mL^{-1}) of sulphadimidine and N_4-acetyl in milk of camels after intravenous administration of SDM as a single or repeated dose treatments at a dose of 50 mg kg^{-1} body weight (n=4 each)

	Single-dose treatment		Repeated-dose treatment	
Milking No.	SDM	N_4-acetyl	SDM	N_4-acetyl
Before dosing	ND	ND	ND	ND
1	10.1±2.1	0.3±0.1	10.3±2.0	0.41±0.2
2	05.3±1.1	0.2±0.1	14.2±2.0	0.71±0.3
3	03.1±0.6	0.1±0.1	18.1±2.5	0.73±0.3
4	02.1±0.5	ND	16.1±2.2	0.68±0.4
5	01.6±0.4	ND	17.2±2.5	0.70±0.2
6	01.2±0.4	ND	16.0±2.5	0.69±0.3
7	00.4±0.2		12.3±2.0	0.43±0.2
8	0.26±0.1		10.1±2.1	0.39±0.2
9	00.1±0.1		6.20±1.1	0.31±0.1
10	ND		3.10±0.6	0.23±0.1
11	ND		2.30±0.8	ND
12	ND		1.60±0.4	ND
13			1.10±0.4	ND
14			0.40±0.1	
15			0.21±0.1	
16			ND	
17			ND	
18			ND	

ND: not detected or below assay sensitivity.

Table 2: Percentage binding of sulphadimidine and N_4-acetyl to plasma and milk proteins (n=4 each)

	Single-dose treatment		Repeated-dose treatment	
Samples	SDM (%)	N_4-acetyl (%)	SDM (%)	N_4-acetyl (%)
Plasma	85±3.1	83.1±3.3	51.3±2.1	46.4±2.1
Milk	41.1±1.6	16±1.8	44.2±2.0	19.9±1.7

DISCUSSION

Intravenous single-dose treatment or repeated-dose treatments with sulphadimidine produced increased concentration of SDM and its metabolite N_4-acetyl in the milk of camel. Injection of sulphadimidine to cattle and sheep by different routes have also produced SDM in milk[8]. Since the sodium salts of SDM is basic in nature they tend to distribute more readily into milk due to pH partioning phenomenon[9]. The pH of milk is acidic (6.6), therefore, SDM will ionize and be excreted in milk.

Residues of SDM in milk must be controlled as recent evidence indicating that SDM may be carcinogenic in human consuming small amounts over long period of time[10]. The primary reason for the occurrence of SDM withdrawal residues in milk were the failure to observe drug time when drug concentration is at Maximum Residue Limit (MRL). The MRL in milk was suggested to be 0.1 μg mL^{-1}[11]. Depletion of SDM to MRL of 0.1 μg mL^{-1} in this study occurred five days post injection in single-dose treatment or five days after the last injection in repeated-dose treatment suggesting that five days could be considered as withdrawal period in milk of camels. For dairy cows a period of 3-4 days was suggested as withdrawal period in milk[8].

In repeated-dose treatments the percentage protein binding for SDM and N_4-acetyl was relatively less than in single-dose treatment. Similar observations at high and low plasma concentration of SDM have been reported[12]. A saturation of protein binding sites has to be assumed and SDM may compete with its metabolite for the same binding site[8]. The fact that metabolite concentrations in milk did not exceed those of parent drug and milk protein binding for metabolite was very low, suggests that monitoring of sulphadimidine in milk of camel could be limited to SDM alone.

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