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Original article

The effect of intramuscular injection of spiramycin at therapeutic dose on some blood biochemical and hematological parameters in Assaf sheep

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ABSTRACT

Spiramycin is used to treatment of different bacterial and protozoal infection in different animal species including sheep, to the authors' knowledge there are no studies about effects of spiramycin in sheep blood biochemical and hematological parameters. This study was designated to determine the effects of spiramycin intramuscular treatment at therapeutic dose (64,000 IU/kg) for five days in some blood biochemical and hematological parameters in healthy Assaf sheep (n=8). The results showed that spiramycin treatment caused decrease in calcium and creatinine level (P<0.05) without significant change in albumin, total protein, magnesium, glucose and the adjusted calcium level (P>0.05). After treatment, hematological parameters tend to decrease toward normal references range of red blood cell count, haemoglobin concentration, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration and red blood cell distribution width (P<0.05). No changes were observed in hematocrit, mean corpuscular volume, platelet count and mean platelet volume (P>0.05). All the measured biochemical and hematological parameters were in the normal references range after the treatment. These results suggested that spiramycin given in therapeutic regimen to healthy Assaf sheep caused only minor inconclusive changes in the measured hematological and biochemical profiles; and thus can be used safely in treating susceptible infections in sheep. These results might be accepted as a starting point for future experiments to evaluate the effects spiramycin on the different systems and

parameters.

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1. Introduction

Spiramycin is a macrolide antibiotic produced from fungus species *Streptomyces ambofaciens*, it is exhibit bacteriostatic action by binding 50S bacterial ribosomal subunit; inhibit protein synthesis in susceptible microorganisms (Abou-Zeid, 1980). Spiramycin is used for the treatment and control of a number of bacterial, mycoplasmal and Toxoplasma infections in human (Gratzl et al., 2002), (Al-Zanbagi, 2007), dog (Pennisi *et al*., 2005), cattle (Pyörälä and Pyörälä, 1998), pigs (Nielsen and Gyrd-Hansen, 1998), poultry (Arzey and Arzey, 1992) and sheep (Cester *et al.,* 1990). It is available for uses in veterinary medicine and as feed additive in United State and Europe (Barton, 2000).

Acute oral toxicity has been reported in mice, rats and dogs after spiramycin treatment (Yankell, 1974), induce hepatotoxicity in human (Saab and Mroueh, 2002) (Denie *et al*., 1992), also allergic dermatitis and asthma was reported in human who handling poultry feed containing spiramycin (Davies and Pepys, 1975). Hematological changes after spiramycin administration was observed in human, characterized by alteration in red blood cell morphology that showed polychromatophilia, poikilocytosis, Heinz bodies, bite cells and uneven distribution of haemoglobin in red blood cells (hemighosts) (Sarma 1997).

In spite of clinical uses of spiramycin in sheep and other animals, there is no available data investigate the ability of spiramycin to induce changes in biochemical and hematological parameters after treatment at therapeutic doses. Our study aims to fill this gap with such knowledge; since blood biochemical and hematological parameters are used in diagnosis and prognosis in clinical situation, the veterinarian must take into account the possible alterations caused by spiramycin to rule out its effects. In this study, the possible changes in blood biochemical and hematological values after spiramycin treatment at therapeutic dose were studied

2. Materials and methods

2.1. Animals

Eight Assaf male sheep appear clinically normal and weighted 40 to 50 kg was used in this study. Animals were housed outdoor in at the farm of An Najah National University–Khadoury in Tulkarm-Palestine. Animals were fed on alfalfa hay and a concentrated grain ration. Water was supplied ad libitum.

2.2. Drug

Spiramycin (SpiramycinDana®) as adipate obtained in the form of 100 milliliters (mL) bottle, each mL contains 600,000 IU spiramycin, manufactured by Dana Veterinary Drugs Factory, Nablus-Palestine. This drug is marketed and prescribed in Palestine.

2.3. Experimental design

Spiramycin was injected intramuscularly in the neck muscle, a dose 64,000 IU/kg at intervals of 24 hours at 10-11 A.M. for five consecutive days. Blood samples were obtained from jugular vein in heparinised tubes (Vacuette®, Greiner Bio-one GmbH, St. Gallen, Switzerland) at day 0 (before drug administration) and after the five days of treatment. Plasma was separated and collected by centrifugation at 1,100 x g (3500 rpm) for 20 min, then directly used for measurement of creatinine, albumin, total protein, calcium, magnesium and glucose, by spectrophotometer using commercial laboratory kits (BioSystem S.A., Barcelona, Spain) and according to kits instruction. Globulin and Albumin/Globulin (A/G ratio) were calculated as:

Globulin = Total protein – Albumin and A/G ratio is equal to Albumin/Globulin.

Hematological parameters Red Blood Cell (RBC) Count, Haemoglobin (Hgb), hematocrit (Hct), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC), RBC Distribution Width (RDW), Platelet Count (PLT) and Mean Platelet Volume (MPV) were evaluated on the automated hematology counter Hemavet® 950 FS (Drew Scientific, Inc, Waterbury, CT)

2.4. Statistical analysis

Paired sample t test was used to evaluate the changes after spiramycin treatment compared to base line before treatment (day 0), $SPSS_{10.0}$ was used for statistical analyses and values were expressed as mean ± standard error of the mean (SEM). Data were considered significant at $P<0.05$.

3. Results and discussion

Changes in biochemical and hematological parameters after five days of spiramycin administration compared to day 0 were shown in Tables 1 and 2. Values showed various changes, some of them did not vary at all. Only values that exhibited changes will be discussed.

3.1. Biochemical evaluation

Spiramycin caused significant decreases in plasma creatinine and calcium level after five days of administration compared to day 0 ($P<0.05$); however both still with normal range. There was no significant change in total protein, albumin, globulin, A/G ratio, magnesium and glucose ($P<0.05$) (Table 1).

Creatinine originates from the conversion of creatine in muscle at a daily constant and uniform rate, it is freely filtered by the glomerulus and small amount is secreted by proximal tubules in the kidney and not reabsorbed by the tubules. The level of creatinine is related to age, sex and muscle mass and renal clearance (Bickhardt and Düngelhoef, 1994). The decrease in plasma creatinine after spiramycin treatment was attributed to increase in renal clearance rate of creatinine, this suggests that alteration of renal functions or change in blood filtration and clearance process in kidney did not occur. At any rate, there is no clinical significance of decrease in creatinine level (Kerr, 1991) as its level still at the baseline of reference range.

Although total protein was low, globulin was high with high A/G ratio at day 0, which indicate subclinical infection or gastrointestinal parasitic manifestation (Chaichisemsar *et al.*, 2011) administration of spiramycin for five days did not cause any significant changes in these parameters.

Decrease blood calcium level in the present study was attributed to decrease in plasma albumin level. Majority of calcium in blood is bound to albumin but the unbound calcium is the most important physiologically; when albumin is low, the total calcium level may be misleading and correction calculation needs to be made, adjusted calcium level was calculated according to the following formula (Duncan *et al*., 1994):

Adjusted calcium (mg/dl) = 3.5 - albumin (g/dl) + measured calcium (mg/dl).

As shown in table 1, the corrected serum calcium level is not significantly differing than the baseline level at day 0 ($P>0.05$), this indicated that the decrease in blood calcium attributed to decrease in albumin. The measured plasma calcium level within reference range before and after treatment excludes spiramycin effect.

3.2. Hematological evaluation

Changes in Hematological values after five days of spiramycin administration compared to baseline values before treatment (day 0) are shown in Table 2.

After five days of spiramycin treatment RBC count, MCH, MCHC and RDW showed statistically significant decrease when compared with baseline level before treatment ($P<0.05$), while MCV increased significantly ($P<0.05$). There were no any significant changes of Hgb, Hct, PLT and MPV ($P>0.05$).

Hematological parameters in this study indicate that there is tendency toward a decrease of red blood cell count, MCH, MCHC and RDW after five days of spiramycin administration, these values were initially high and fall within the normal range for sheep. The changes in hematological values toward normal reference range and the absence of clinical signs of hemolytic or hemorrhagic anemia might be an indication for the lack of depression effect of spiramycin in erythrogenesis.

4. Conclusion

It could be concluded that spiramycin given in therapeutic doses for five days to healthy Assaf sheep caused only minor inconclusive changes in the measured hematological and biochemical profiles in treated animals; and thus can be used safely in treating different susceptible infections in sheep. These results might be accepted as a starting point for future experiments to evaluate the effects spiramycin on the different systems and parameters.

Table 1
Change in some blood biochemical after five days of spiramycin treatment (64,000 IU/kg) to 8 male Assaf sheep compared to values before treatment (mean ±SEM).

Parameter	Day 0	After five days	Reference Values (unit)**
Creatinine	0.863 ± 0.06	0.49 ± 0.11*	0.9-2.0 (mg/dl)
Total protein	4.93 ± 0.24	5.13 ±0. 37	5.9-7.8 (mg/dl)
Albumin	3.32 ± 0.15	3.05 ± 0.16	2.7-3.7 (mg/dl)
Globulin	16.0 ± 2.442	2.07 ± 0.304	3.2-5.0 (mg/dl)
A/G ratio	2.48 ± 0.422	2.01 ± 0.579	0.74-0.84 (%)
Calcium	11.75 ± 0.25	9.46 ± 0.81*	9.3-11.7 (mg/dL)
Corrected Calcium	11.87 ± 0.32	9.93 ± 2.38	9.3-11.7 (mg/dL)
Magnesium	1.75 ± 0.15	1.33 ± 0.15	2.0-2.7 (mg/dL)
Glucose	80.50 ± 6.22	89.74 ± 3.49	44-81(mg/dL)

* indicate significant change from day 0 throughout paired T test ($p<0.05$).
**Data from The Merck Veterinary Manual. Reference Guides [on line] (2011),
URL: http://www.merckvetmanual.com/mvm/index.jsp?cfile=htm/bc/ref_00.htm

Table 2
Change in hematological values after five days of spiramycin treatment (64,000 IU/kg) to 8 male Assaf sheep compared to values before treatment (mean ±SEM).

Parameter	Day 0	After five days	Reference Values (unit)**
RBC count	13.39 ± 0.40	12.80 ± 0.48*	9.0-15.0 ($x10^6$/µl)
Hgb	22.84 ± 2.65	10.36 ± 0.25*	9.0-15.0 (g/dl)
Hct	31.89 ± 0.95	33.11 ± 1.12	27.0-45.0 (%)
MCV	23.88 ± 0.62	26.04 ± 0.92*	28.0-40.0 (fl)
MCH	17.08 ± 1.95	8.56 ± 0.29*	8.0-12.0 (pg)
MCHC	71.69 ± 8.10	31.39 ± 0.63*	31.0-34.0 (g/dl)
RDW	25.99 ± 0.58	22.36 ± 0.58*	12.0-27.0 (%)
PLT	736.9 ± 33.06	546.14 ± 74.34	250-750 ($x10^3$/µL)
MPV	9.84 ± 0.348	9.37 ± 0.298	5.00-20.0 (fl)

* indicate significant change from day 0 throughout paired T test ($p<0.05$).
**Data from The Merck Veterinary Manual. Reference Guides [on line] (2011),
URL: http://www.merckvetmanual.com/mvm/index.jsp?cfile=htm/bc/ref_00.htm

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