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Kısa Bildiri ***Short Communication***

Comparative Study of Erythrocyte Sedimentation Rate after Aminoglycoside and Aminocyclitol Treatment in Goats (*Capra hircus*)

Toncho DINEV[1], Dian KANAKOV[2], Georgi BEEV[1], Nikolina RUSENOVA[3], Stefan DENEV[1]*

[1]Faculty of Agriculture, Department of Biochemistry, Microbiology and Physics, Trakia University, 6000 Stara Zagora, Bulgaria
[2]Faculty of Veterinary Medicine, Department of Internal Diseases, Trakia University, 6000 Stara Zagora, Bulgaria
[3]Faculty of Veterinary Medicine, Department of Veterinary Microbiology, Infectious and Parasitic Diseases, Trakia University, Stara Zagora 6000, Bulgaria

****Sorumlu Yazar / Corresponding Author:***
Toncho DINEV
e-mail: dinev_sz@mail.bg

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Abstract

The aim of the present study was to follow up the erythrocyte sedimentation rate (ESR) in healthy female goats during and after 5-day parenteral treatment with amikacin (10 mg/kg), tobramycin (5 mg/kg), apramycin (20 mg/kg), gentamicin (4 mg/kg), kanamycin (10 mg/kg) and spectinomycin (20 mg/kg). Gentamicin and tobramycin caused an initial increase followed by a significant decrease of ESR on the 5th day for gentamicin and the 10th day for tobramycin, respectively, followed by recovery after the treatment. Reversely, amikacin and especially spectinomycin produced an increase of ESR without recovery several days post treatment. Kanamycin caused decrease of ESR on the 5th day without recovery in the subsequent days. Only apramycin did not give rise to increasing of ESR. In conclusion, the aminoglycosides, especially tobramycin and gentamicin, caused more severe alterations of ESR than the aminocyclitols.

Introduction

Erythrocyte sedimentation rate (ESR) is an important routine test in hematology. The increase of ESR is an indicator of inflammation, as well as pregnancy, anemia, kidney diseases or rheumatoid arthritis. Some authors found that the combination of the independent measurements of C-reactive protein and ESR may improve diagnostic sensitivity and specificity for inflammatory diseases (Liu et al., 2013). ESR values are decreased at polycythemia, leukemia and congestive heart failure. Aminoglycosides and the related in chemical structure aminocyclitols are used very often in the treatment of inflammatory diseases (Dowling, 2013). In order to minimize the adverse effects of the drugs now they are commonly used once daily in contrast with the previous treatment 2-3 times per day. Given the effectiveness of these drugs is concentration-dependent and count on rapid achievement of high serum concentrations, the first dose can be injected intravenously, and the next ones – intramuscularly (Lacy et al., 1998). Well known are the nephrotoxic changes caused by these antibiotics in high doses (Hottendorf and Gordon 1980; Schentag et al., 1981) and in this respect there are comparative trials (Brion et al., 1984; Hottendorf and Gordon, 1980; Rankin et al., 1980; Schentag et al., 1981). However, there are experiments on the impact of low therapeutic doses of these antibiotics on biochemical and hematological parameters (Dinev et al., 2005; Yazar et al., 2003). Data for ruminants, particularly goats are also limited (Dinev et al., 2005; Lashev and Lasarova, 2001; Sumano et al., 2005).

There are no data on the response of ESR at application of therapeutic doses of aminoglycosides and aminocyclitols. Since the drugs are used for treatment of infections that also cause changes in ESR, if the physician does not take into consideration the possible alterations caused by the aminoglycosides, an incorrect diagnosis

may be made and an improper medication could be administered. The available literature lacks reference values of ESR in goats.

The aim of the present study was to follow up the ESR changes during and after 5-day treatment with therapeutic doses of these antibiotics.

Materials and Methods

Each experiment was conducted on a group of 6 non-pregnant and non-lactating female goats (Bulgarian white dairy goat breed) at the age of 1.5-3 years. During the trials the goats weighted 43.71 ± 3.31 kg (mean ± SD). The animals were housed outdoors in identical conditions, according to the requirements of the species. They were fed on alfalfa hay and a concentrated grain ration. Water was supplied *ad libitum*.

The experiment complies with the current laws of the Republic of Bulgaria. The animals were treated at intervals of 24 h for 5 consecutive days. Each group was administered with only one antibiotic. The first dose was injected intravenously and the next 4 doses were injected intramuscularly (Table 1).

Blood samples for ESR evaluation were collected before the experiment, on days 1, 3 and 5, and twice after the 5-day treatment (on days 8 and 12 for amikacin, on days 10 and 17 for kanamycin, and on days 10 and 15 for tobramycin, apramycin, gentamicin, and spectinomycin). Blood samples were obtained before the goats were injected with the corresponding daily dose of the antibiotic. The volume of blood samples was 4 ml. ESR (mm) was measured according to Westergren method.

Statistical analysis was done by "Statmost for Windows" software (DataMost Co., USA, 1994), and the values were compared using Tukey's test. Significance was set at $P<0.05$.

Table 1. Antibiotics used in the study.

Antibiotic	Drug form (company, country)	Drug conc. (%)	Dose (mg/kg)
Amikacin	Ampoules amikacin sulphate (Sopharma, Bulgaria)	25	10
Tobramycin	Substance tobramycin 983 μg/mg (Actavis, Bulgaria)	10	5
Apramycin	Phials apramycin sulphate 50 mL (Actavis, Bulgaria)	20	20
Kanamycin	Phials kanamycin sulphate100 mL (Alphasan, Holland)	25	10
Gentamicin	Phials gentamicin sulphate50 mL (Actavis, Bulgaria)	10	4
Spectinomycin	Phials spectinomycin 100 mL (Ceva, France)	10	20

Results

All tested antibiotics caused statistically significant changes of ESR values with the exception of apramycin (Table 2). The most significant alterations were detected after gentamicin and tobramycin treatment. Also, these two antibiotics caused similar deviations in the values of the studied parameter. They lead to the initial significant increase of ESR, followed by its decrease (on the 5th day of gentamicin and on the 10th day of tobramycin treatment) and restoration on the 15th day. Increase of ESR during the entire period of treatment is caused by amikacin and spectinomycin, and after amikacin application the original values of the parameter were not restored. Changes, especially after treatment with amikacin, were lesser, although there was a significant difference. Kanamycin caused a decrease of ESR in the last days of treatment, with no tendency to recovery. On the other hand apramycin brought about the least pronounced and insignificant changes of ESR.

Discussion

The statistically significant increase of ESR values on the 3rd day of gentamicin treatment obtained in our study is consistent with the experimental results of Dhar et al. (2013) that treated rats with a high dose of gentamicin (40 mg/kg) for 10 days. These authors interpret it as one of the indicators for nephrotoxicity. Such a significant increase of ESR reported Mumtaz et al. (2014) after treatment of rabbits with gentamicin in dose 80 mg/kg. In our study the trends are miscellaneous - gentamicin after an initial increase of ESR caused significant decrease of the parameter on the 5th day, followed by a partial recovery of the baseline values on the 10th day and full recovery on the 15th day. Almost identical changes were observed after tobramycin administration. The reason for such variability is probably the use of much lower (therapeutic) doses of the antibiotics, wherein the trends observed are not sufficiently stable and defined and there is no indication for nephrotoxicity.

Table 2. Changes in ESR after a 5-day aminoglycoside or aminocyclitol treatment to goats (mean±SEM).

Parameter	Days					
Amikacin	**0**	**1**	**3**	**5**	**8**	**12**
ESR (mm/1h)	11.5±0.89	12.83±0.87	12.17±0.95	12.83±0.75	12.5±0.76	14.17±0.75[1,3,5]
ESR (mm/2h)	22.83±2.06	25.83±1.68[1]	24.5±2.05	26.33±1.89[1]	25.83±1.47	29.17±1.42[1,2,3]
ESR (mm/24h)	103.67±5.68	115.33±3.92[1]	117.5±3.0[1]	114.33±3.41[1]	121±2.18[1,4]	121.83±2.9[1,4]
Tobramycin	**0**	**1**	**3**	**5**	**10**	**15**
ESR (mm/1h)	12.67±0.8	13.5±0.85	14.83±1.38[1]	15.67±1.12[1,2]	5.33±0.42[1,2,3,4]	13.67±1.2[4,5]
ESR (mm/2h)	26±1.53	28±1.46	31±2.82[1]	31.17±2.06[1]	11.33±0.49[1,2,3,4]	29±2.08[5]
ESR (mm/24h)	118.33±2.56	124.33±3.5	124±4.09	126.83±3.94[1]	79.5±3.87[1,2,3,4]	118±4.54[4,5]
Apramycin	**0**	**1**	**3**	**5**	**10**	**15**
ESR (mm/1h)	15.17±2.12	15.5±1.61	14±1.13	16.17±1.56	16.83±1.45[3]	12.67±1.31[2,4,5]
ESR (mm/2h)	32.5±3.83	30.83±3.2	31.17±2.6	33.83±3.27	33±2.88	28.67±2.4
ESR (mm/24h)	124.17±5.64	125.67±4.83	122.5±2.83	125.5±5.67	127.5±4.1	120.67±4.22
Kanamycin	**0**	**1**	**3**	**5**	**10**	**17**
ESR (mm/1h)	18.67±1.84	17.83±1.01	19±1.67	16.17±0.95[1,3]	16.67±1.69	14±0.86[1,2,3,5]
ESR (mm/2h)	36.5±3.17	33.83±1.74	38.5±2.79[2]	33.33±2.06[3]	32.67±3.39[3]	30±1.97[1,3]
ESR (mm/24h)	131.33±3.08	133±3.03	136.5±3.46	130.67±2.82	131.5±4.46	127.83±3.27[3]
Gentamicin	**0**	**1**	**3**	**5**	**10**	**15**
ESR (mm/1h)	15±1.37	16.33±1.5	20.33±1.96[1,2]	8.67±0.84[1,2,3]	11.17±0.91[1,2,3,4]	16.17±0.87[3,4,5]
ESR (mm/2h)	31.67±2.51	34.83±2.85	38.33±3.44[1]	18.67±1.5[1,2,3]	24.17±1.62[1,2,3,4]	33.67±1.41[3,4,5]
ESR (mm/24h)	127±3.75	130.83±3.22	134.83±3.35[1]	100±4.95[1,2,3]	121.83±2.44[2,3,4]	129.33±3.59[4,5]
Spectinomycin	**0**	**1**	**3**	**5**	**10**	**15**
ESR (mm/1h)	12±1.0	16.33±0.71[1]	16.5±1.26[1]	17.33±1.43[1]	14.33±1.82[4]	14.67±1.74[1,4]
ESR (mm/2h)	25.5±1.48	34.83±1.78[1]	33.67±2.58[1]	34±3.12[1]	30.33±3.44[1]	31.17±2.89[1]
ESR (mm/24h)	114.67±3.9	121.17±4.0	131.33±3.96[1,2]	130.33±4.1[1,2]	125.33±4.12[1]	129.33±3.98[1,2]

[1]Significantly different from the control values (day 0), P<0.05; [2]Significantly different from day 1, P<0.05;
[3]Significantly different from day 3, P<0.05; [4]Significantly different from day 5, P<0.05; [5]Significantly different from day 8 or 10, P<0.05.

In our study amikacin caused increase of ESR values, which continued to grow after treatment. The changes in ESR after amikacin administration were not pronounced, although there was a significant difference. Such increase of ESR is reported by Sayarifard et al. (2015) in a child with amikacin induced nephrotoxicity. The analysis of amikacin and gentamicin survey data indicates that in kidney damage along with important biochemical indicators (such as elevation of urea and creatinine concentration), ESR is also increased (Dhar et al., 2013; Mumtaz et al., 2014; Sayarifard et al., 2015). The slight variations of ESR values after amikacin administration

can be explained by the low nephrotoxic potential of this aminoglycoside, less than the same for gentamicin and tobramycin (Hottendorf and Gordon, 1980).

Spectinomycin leads to significant increase of ESR, followed by a trend to recovery of the baseline values. The differences were statistically significant, but not highlighted, probably due to the low potential of spectinomycin to cause changes in biochemical and hematological parameters at therapeutic doses (Dinev, 2007). Apramycin brought about the least pronounced and insignificant changes of ESR. We assume the reason for the less distinct changes of goat´s ESR in aminocyclitol treatment is due to the lack of nephrotoxic potential of the aminocyclitols (Dowling, 2013). Up to now they are no experimental data suggesting nephrotoxic effects after their application, even after high-dose therapy (Novak et al., 1974). Kanamycin caused decrease of ESR values in the last days of treatment, without restoration - a tendency that is generally contrary to the observed in our study. However, differences in the values of ESR, although statistically significant, are not highly expressed. Lack of research data regarding ESR response to spectinomycin, kanamycin and apramycin administration makes difficult the explanation of the somewhat inconsistent trends observed in our study. We assume that this is due to the use of therapeutic doses of antibiotics, which rarely cause pronounced changes.

In conclusion, according to the experimental results gentamicin and tobramycin cause remarkable changes in goat´s ESR, even after treatment with therapeutic doses. This gives grounds to recommend ESR data after treatment with these antibiotics to be cautiously interpreted. Generally, the aminocyclitols cause less pronounced changes in the goat´s ESR than the aminoglycosides.

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