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EFFECTS OF AMINOGLYCOSIDE AND AMINOCYCLITOL ANTIBIOTICS ON BLOOD COAGULATION IN GOATS

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Summary

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The changes in blood coagulation parameters fibrinogen, thrombin time (TT), prothrombin time (PT) and activated partial thromboplastin time (APTT) were followed out after parenteral application of gentamicin (4 mg/kg), tobramycin (5 mg/kg), amikacin (10 mg/kg), kanamycin (10 mg/kg), apramycin (20 mg/kg) and spectinomycin (20 mg/kg) in goats for 5 days. Increased fibrinogen concentrations and reduced PT values were determined. There was a tendency towards increased APTT values whereas TT was not significantly altered. Although statistically significantly changed vs baseline, all variations were within the physiological ranges. It could be concluded that there were not any significant changes in blood coagulation potential in goats that could possibly induce clinical haemocoagulation troubles.

Key words: aminoglycoside antibiotics, goats, haemocoagulation

INTRODUCTION

Aminoglycosides are widely used in veterinary medicine, including in animals with haemorrhagic diathesis. That is why their effect on blood coagulation is important with regard to their choice. The available literature data are however scarce and are predominantly for their effect on thrombocyte function in men (George *et al*., 1998; Davis *et al*., 2004).

There are numerous data about some drugs' effect, including that of antibiotics, on the various stages of haemostasis, (Genua *et al*., 1980; Murer & Siojo, 1982; Cronberg *et al*., 1984; Gentry *et al*., 1992; Wilkens *et al*., 1995; Zimmerman, 2000; Brooks & Catalfamo, 2005). Studies in men and dogs evidence that the use of some antibiotics results in impaired blood coagulation (Genua *et al.*, 1980; Cronberg *et al.*, 1984; Wilkens et al., 1995; Webb *et al.*, 2006). There are data showing that the application of streptomycin, tobramycin and gentamicin could results in thrombocytopenia in men (George *et al.*, 1998; Davis *et al.*, 2004). In ruminants and especially in goats, the effect of aminoglycosides upon haemostasis is not known. Therefore, the aim of the present study was to investigate the effect of six (amikacin, tobramycin, apramycin, gentamicin,, kanamycin and spectinomycin) aminoglycosides and aminocyclitols on some blood coagulation parameters in goats.

MATERIALS AND METHODS

Experimental animals

In this experiment, clinically healthy female Bulgarian White Dairy goats at the age of 1.5–4 years, previously treated against parasites, were used. During the experiment with amikacin, the animals weighed 38.62±3.51 kg, with tobramycin – 43.12±3.39 kg, with apramycin – 44.13 ±3.5 kg, with kanamycin – 45.9±3.51 kg, with gentamicin – 44.92±3.24 kg, and with spectinomycin – 45.5±2.7 kg. The goats were placed under similar standard conditions of feeding and rearing during the entire experimental period.

Drugs

The medicinal products, used in this study, are presented in Table 1.

Experimental design

Each antibiotic was applied in a group of 6 animals at 24-hour intervals for 5 consecutive days. The first day it was administered intravenously in the jugular vein and the other 4 – intramuscularly, in the cervical muscle region. Between the separate experiments, washout periods of 1–2 months for elimination of previously applied antibiotics, were allowed.

In the experiments with tobramycin, apramycin, spectinomycin and gentamicin, blood samples were obtained prior to the treatment (day 0) and at post treatment days 1, 3, 5, 10 and 15, just before the injection. In the trial with amikacin, blood was sampled by days 0, 1, 3, 5, 8, and 12 after applications and throughout that with kanamycin – by days 0, 1, 3, 5, 10 and 17. Blood samples were obtained at 7–8 h AM prior to injection of the respective daily dose with 0.11 mmol/L sodium citrate as anticoagulant, observing the ratio of 9 parts blood and 1 part citrate. They were stored in a refrigerator and analyzed within 2 h after separation of blood plasma by centrifugation at 3000 rpm. The parameters of haemostasis, resp. blood coagulation – fibrinogen in g/L, activated partial thromboplastin time (APTT) in s,

Table 1. Brand names and dosages of used drugs

Antibiotic	Brand name	Concentration of the solution	Dosage (mg/kg)
Amikacin	Amikacin sulfate ampules 2 mL (Sopharma)	25%	10
Tobramycin	Tobramycin sulfate with activity 983 μg/mg (Actavis)	10%	5
Apramycin	Apramycin sulfate vials 50 mL (Actavis)	20%	20
Gentamicin	Gentamicin sulfate vials 50 mL (Actavis)	10%	4
Kanamycin	Kanamycin sulfate vials 100 mL (Alphasan)	25%	10
Spectinomycin	Spectinomycin vials 100 mL (Ceva)	10%	20

prothrombin time (PT) in s and thrombin time (TT) in s, were analyzed on a coagulometer KC1A (Amelung, Germany) with commercial (Human Diagnostica GmbH, Germany).

Statistical analysis

Data were analyzed by the Tukey's test, using the StatMost for Windows software (DataMost Co., USA, 1994). The results are presented as mean ± SEM.

RESULTS

In different post treatment periods all studied antibiotics with the exception of gentamicin, provoked statistically significant increase in fibrinogen values, that was the most expressed between the 5th and the 10th day (Table 2). By day 15, there was a tendency towards restoration to values, close to the initial ones. After the application of tobramycin and apramycin they were lower, and following spectinomycin administration – higher than baseline.

The changes in APTT were various, in a tendency towards increased values in most cases – after the tobramycin treatment – between the 5th and the 10th day, and after kanamycin and spectinomycin treatments – during the entire period of the study (Table 2). Apramycin administration resulted in lower APTT after the 5th day to the end of the study period. After the treatments with amikacin and gentamicin, no changes were observed.

In all studied antibiotics with the exception of spectinomycin, PT exhibited a trend towards reduction, most evident by the 3rd–5th day (Table 2). This was also observed 12 days after amikacin treatment and 15 days after apramycin administration. By the 15th day of the experiment with tobramycin and the 17th day of that with kanamycin, the opposite trend was present – PT prolongation.

All antibiotics caused mainly weak and inconsistent changes in TT despite the statistically significant differences in some periods of the experiment (Table 2). The amikacin and kanamycin values were lower by days 12 and 15 respectively whereas 15 days after tobramycin administration, TT was prolonged compared to baseline.

DISCUSSION

The results about the alterations in blood coagulation after treatment of goats with aminoglycosides and aminocyclitols for 5 consecutive days showed that the studied parameters were within the reference range for this animal species (Georgiev *et al.*, 2002). The changes during the treatment with these drugs, related to increased fibrinogen and shorter PT (characterizing the second stage of haemostasis) allowed to assume that there was an increased haemocoagulation potential in animals.

In our experiments, APTT, that indicates the activity of the first stage of the intrinsic blood coagulation system, revealed a prevailing tendency towards increased values, i.e. prolongation of time needed to blood to coagulate.

For TT, there was not a clear trend towards either increase or decrease.

The lack of literature data about the effect of aminoglycosides upon blood coagulation parameters in domestic animals does not permit to make some comparisons. The studies upon the influence of streptomycin, tobramycin and gentamicin on thrombocyte counts in humans (George *et al.*, 1998; Davis *et al.*, 2004) show that thrombocytopenia occurs exceptionally rarely and it was considered to be immune-mediated. That is why, we could assume

Table 2. Values of blood coagulation parameters (mean±SEM) in goats after adminsitration of aminoglycosides

Antibiotic		Days post administration					
Amikacin		0	1	3	5	8	12
Para-meters	F, g/L	1.99±0.08	2.28±0.17[1]	2.22±0.12	2.32±0.14[1]	2.56±0.11[1,2,3]	2.05±0.14[2,4,5]
	TT, s	11.8±0.2	11.7±0.3	11.3±0.3	10.7±0.4[1,2,3]	11.6±0.2[4]	10.7±0.2[1,2,3,5]
	PT,s	16.3±0.4	15.1±0.3[1]	14.4±0.4[1,2]	14.7±0.3[1]	15.8±0.1[2,3,4]	15.6±0.3[1,3,4]
	APTT, s	37.5±1.9	36.0±1.6	34.7±1.0	35.1±3.0	34.1±2.4	34.4±2.8
Tobramycin		0	1	3	5	10	15
Para-meters	F, g/L	2.50±0.25	2.45±0.17	3.00±0.2[1,2]	3.23±0.19[1,2]	2.62±0.14[3,4]	2.13±0.14[1,3,4,5]
	TT, s	11.1±0.5	12.3±0.5[1]	11.7±0.4	12.2±0.6[1]	11.9±0.4	12.6±0.6[1,3]
	PT,s	17.4±0.3	17.6±0.4	16.2±0.4[1,2]	17.2±0.2[3]	17.7±0.3[3]	18.3±0.1[1,2,3,4,5]
	APTT, s	32.6±1.7	33.2±1.8	34.1±1.9	35.7±1.7[1]	36.1±1.6[1]	35.1±1.3
Apramycin		0	1	3	5	10	15
Para-meters	F, g/L	2.55±0.21	2.44±0.2	2.9±0.42[2]	2.61±0.23	2.37±0.12[3]	2.20±0.16[3]
	TT, s	11.7±0.4	12.1±0.5	14.7±1.3[1,2]	12.4±0.2[3]	11.2±0.5[3,4]	11.9±0.2[3]
	PT,s	18.2±0.4	18.9±0.5	17.6±0.5[2]	16.4±0.5[1,2,3]	16.8±0.4[1,2,3]	17.4±0.3[1,2,4]
	APTT, s	36.4±1.2	37.7±1.5	35.1±2.9	31.8±2.5[1,2]	30.9±1.7[1,2,3]	32.0±1.2[1,2]
Kanamycin		0	1	3	5	10	17
Para-meters	F, g/L	2.46±0.07	2.82±0.19[1]	2.72±0.21	2.91±0.15[1]	2.92±0.29[1]	2.46±0.14[2,4,5]
	TT, s	14.5±0.7	14.1±0.6	12.8±0.6[1,2]	11.0±0.4[1,2,3]	11.9±0.3[1,2,3]	11.8±0.4[1,2,3]
	PT,s	16.2±0.2	15.5±0.3[1]	16.1±0.3[2]	15.2±0.2[1,3]	15.9±0.6[4]	17.2±0.1[1,2,3,4,5]
	APTT, s	31.0±1.5	34.6±1.3[1]	35.3±1.3[1]	34.8±1.3[1]	36.4±1.1[1]	36.8±1.1[1]
Gentamicin		0	1	3	5	10	15
Para-meters	F, g/L	2.02±0.15	2.03±0.12	1.96±0.12	2.08±0.13	2.24±0.12[3]	2.02±0.21
	TT, s	11.7±0.4	11.9±0.6	13.2±0.5[1,2]	12.3±0.4[3]	12.4±0.4[3]	12.0±0.5[3]
	PT,s	17.9±0.6	17.4±0.4	17.1±0.3	16.0±0.5[1,2,3]	16.6±0.4[1]	17.5±0.5[4,5]
	APTT, s	36.4±1.4	37.2±1.4	38.7±1.5	38.6±0.6	37.4±1.6	39.7±1.1[1,2,5]
Spectinomycin		0	1	3	5	10	15
Para-meters	F, g/L	2.23±0.1	2.09±0.16	2.58±0.31	3.13±0.26[1,2,3]	2.70±0.23[2]	2.70±0.43[2]
	TT, s	12.9±0.5	12.2±0.3	12.2±0.3	12.9±0.6	12.7±0.5	13.7±0.3[1,2,3,4,5]
	PT,s	16.6±0.4	16.9±0.3	15.9±0.5[2]	15.9±0.3[2]	17.2±0.6[3,4]	16.3±0.1[5]
	APTT, s	35.6±1.0	39.7±1.0[1]	41.3±1.3[1]	41.9±1.9[1]	39.6±1.1[1]	38.9±1.7[1,3,4]

F=fibrinogen; TT=thrombin time; PT=prothrombin time; APTT=activated partial thromboplastic time; [1] P<0.05 vs day 0; [2] P<0.05 vs day 1; [3] P<0.05 vs day 3; [4] P<0.05 vs day 5; [5] P<0.05 vs days 8 or 10.

that aminoglycosides are relatively safe with regard to their effect on blood coagulation.

CONCLUSION

On the basis of the present results, a comparison of studied antibiotics with regard to their effect upon haemostasis in goats could be hardly made. In all cases, the changes were not consistent despite the statistically significant differences vs baseline. Therefore, significant alterations of the blood coagulation in goats and consequently, clinically manifested changes could hardly be expected.

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