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## Changes in haemato-biochemical and urine indices in response to the intravenous administration of amikacin

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### Abstract

Amikacin is the most commonly used aminoglycoside to treat a variety of serious infections caused by aerobic gram-negative bacteria, as well as mycobacteria and Nocardia in animals. Due to its inherent property of being refractory to most of the aminoglycoside modifying enzymes. These antibiotics is their relatively low therapeutic index. The use at therapeutic dosage may lead to adverse changes in haemato-biochemical indices, especially with those connected with kidney and liver function. The aim of the present study was to determine the changes in some and haemato-biochemical parameters during 5 days intravascular administration with amikacin (10 mg/kg bwt) in four healthy non lactating female goats. The results of these studies indicated that in healthy goats, at the therapeutic dosage, caused significant ( $p < 0.05$ ) rise in serum BUN and creatinine levels, but did not produce any significant changes on blood Hb, PCV, TEC, TLC, lymphocyte, monocyte, eosinophil, basophil and neutrophil and the serum albumin, globulin, total protein, bilirubin, cholesterol and triglyceride level. Amikacin also caused significant ( $p < 0.05$ ) rise in serum enzyme ALT, AST and ALP level. On the whole, the results of these studies demonstrate that amikacin did not have much potential for altering the major changes in haemato-biochemical and urine indices in female goats after administration of amikacin at therapeutic dosage.

**Keywords:** amikacin, goats, intravascular, haemato-biochemical, dosage

### Introduction

Amikacin is the most widely used semisynthetic aminoglycoside [1]. Due to its property of being refractory to most aminoglycoside modifying enzymes [2, 3, 4]. Amikacin has been successfully used to treat other aminoglycoside resistant infections [4, 5]. The optimal antibacterial effects occur when the maximum concentration in serum is 8 to 10 times higher than the minimal inhibitory concentration [6]. Amikacin alone or in combination with other antibiotics is used to treat a variety of serious infections caused by aerobic gram-negative bacteria, as well as mycobacteria and Nocardia [4, 7, 8]. This antibiotic is also essential in the treatment of life-threatening infections [5, 9, 10]. Amikacin is mainly administered intravenously, intramuscularly, through nebulization [11, 12, 13]. Other routes of administration for specific infections are intrathecal or intraventricular [14, 15]. Amikacin is mostly administered as a weight-based dose divided in two applications per day or as a once-daily strategy, with this latter strategy being the preferred option [7, 16, 17].

Since amikacin exhibits the toxic effects common to aminoglycosides, i.e., ototoxicity and nephrotoxicity, the dose regime to maximize therapeutic outcomes and minimize adverse consequences is of great importance [18]. Unfortunately, the recent rise in resistance to amikacin limits the effectivity of many interventions during outbreaks of infection [1, 19, 20]. Although it has been successful in treating infections caused by multidrug resistant strains [9, 21, 22]. The characteristic feature of these antibiotics is their relatively low therapeutic index. The use of therapeutic doses may lead to adverse changes in haemato-biochemical and urine indices, especially with those connected with kidney and liver function. The physician therefore has to create a proper balance between their use as an antibiotic and these adverse effects to avoid any occasion of iatrogenicity or improper medication. In veterinary medicine such data exist mainly for other aminoglycoside antibiotics because of its wide application and its considerable nephrotoxic potential [23, 24]. Such information, considering amikacin is rather scarce for goats.

The results of the present study would, certainly facilitate in understanding the possible hazards of antibiotic, if any, which will help in recommending its judicious use in the field condition.

## Materials and Methods

### Experimental animals

The experiment was performed in four clinically healthy female non lactating goats of Sirohi breed between 1 to 2 years of age and 15 to 25 kg body weight. The experimental animals were maintained in the College of Veterinary Science and Animal Husbandry, Rewa (M.P.) under uniform managemental conditions. The animals were dewormed before the commencement of the experimental study. During this entire period of experiment, animals were subjected to regular clinical examination, and maintained on dry as well as green fodder, concentrate and a routine grazing for at least 4 to 5 hours every day. Clean potable drinking water was provided *ad libitum*. All the animals were apparently healthy during the study. The experimental protocol for general procedure and use of animals for conducting the present study has been reviewed and approved by the Institutional Animal Ethics Committee (IAEC), College of Veterinary Science & AH, Rewa, Madhya Pradesh, India,

### Drugs

Injectable commercial preparation containing amikacin equivalent to 250 mg/ml (Amidac India) was used in the present investigation. Amikacin was administered at the dose rate of 10 mg/kg bwt intravascular in each of four healthy goats once daily at intervals of 24 hours for five consecutive days [25].

### Blood sampling and processing

Blood samples for evaluation of haemato-biochemical parameters were collected on the 0 (one day before experiment), 2<sup>nd</sup>, 4<sup>th</sup> and 6<sup>th</sup> days (one day after experiment). Blood samples were collected into two tubes. The first tube contained anticoagulant (Na<sub>2</sub> EDTA) for complete blood count (CBC) analysis. Blood samples in the other tube were left for a short of time to allow clotting. The serum samples were obtained by centrifugation at 3000 rpm for 20 min. A clear serum samples were kept in a deep freeze for biochemical analysis. However determination of enzymes activity were carried out on fresh serum samples.

### Haematological Parameters

The whole blood was used for the estimation of haemoglobin (Hb), packed cell volume (PCV), total erythrocyte counts/red blood cell count (TEC/RBC) and total leucocytes counts/white blood cell count (TLC/WBC). The haematological parameter was carried out as per the procedure mentioned by Jain [16].

### Biochemical Parameters

Serum was separated from the blood without anticoagulant from the experimental animals. The serum was used for the estimation of BUN, creatinine, bilirubin, albumin, total protein, cholesterol, triglycerides, aspartate aminotransferase (AST), alanine amino transferase (ALT), alkaline phosphatase (ALP) either on the day of collection or stored at -18 °C for subsequent analysis. Serum biochemical Parameters was determined using Erba EM200 Automated Biochemistry Analyzer. Transasia (ERBA) Biochemistry Test Kits were

used for the analysis as per the manufacturer's instruction.

### Urine sampling and processing

The urine samples were collected in sterile tubes from the experimental animals at predetermined day after multiple once daily amikacin administration and then preserved in thymol (a small crystal of thymol for 5-10 ml urine). Urine samples collected was used to determine the bile salt, ketone body, albumin, RBC, caste, crystal and other parameters [27].

### Statistical analysis

Data are presented in Means±Standard Error (SE). The data was analyzed using statistical tools (SPSS version 16). ANOVA followed by Multiple Range, Duncan's Test was used for multiple comparisons. Statistical differences were determined at the 5% level of significance.

### Result and Discussion

In our present study, goats were used to observe the haemato-biochemical alterations after administration of amikacin at therapeutic dosage. Various haemato-biochemical parameters were performed for evaluation of the functions of the organ. Aminoglycosides are commonly used as a therapeutic agent against infections. But long-term exposure of aminoglycosides in 30% cases may induce hepato-renal toxicity [28, 29].

The food consumption, water intake, general behavior and body weight of the goat did not show any apparent change during the amikacin administration. The level of Hb, PCV, TEC, TLC, lymphocyte, monocyte eosinophil, basophil and neutrophil count did not observe any significant ( $p < 0.05$ ) changes during administration of amikacin (Table 1). Whereas, our findings are in contrary to the results of Dinev *et al.* (2005) [30] who reported that there is tendency toward a decrease of erythrocyte count, haemoglobin concentration and haematocrit percentage after 5 days intramuscular treatment with amikacin (10 mg/kg bwt) in healthy female goats. Contrary result also observed by Jannat *et al.* (2018) [31], who reported significantly reduced the TEC, TLC and Hb after gentamicin administration. Another findings were reported by Lijana and Williams (1986) [32] after a long term exposure of aminoglycosides in high dose affects the haemopoietic cells in the bone marrow and decrease erythrocyte production.

The serum enzymes AST, ALT and ALP also showed significant ( $p < 0.05$ ) rise after administration of amikacin. Whereas other serum parameters *viz.*, albumin, globulin, total protein, bilirubin, cholesterol, triglyceride level did not show any significant ( $p < 0.05$ ) changes but the BUN and creatinine were significantly ( $p < 0.05$ ) increased after the amikacin administration (Table 2). In the present study, a significant increase of AST, ALT and ALP was observed and the increased value is essential indicator of initial hepatocellular damage (Michalowicz and Duda, 2007) [33]. These finding are in close agreement with Anitha *et al.* (2016) [34] who reported that cholesterol, total triglycerides, bilirubin, total protein and albumin did not show any significant change after amikacin administration.

It was postulated that amikacin treatment caused elevation in serum BUN and creatinine concentration and AST, ALT and ALP enzyme activity associated with pathological changes in liver and kidney (Atef *et al.*, 1992) [35]. It was showed that amikacin could induce renal toxicity and significant increase in the level of ALT (Kadkhodae *et al.*, 2005) [36]. The recorded increased level of ALT indicates functional disorders of the liver as postulated by another researcher

(Mayne, 1994) [37]. Increased level of serum enzymes due to amikacin treatment induced oxidative injury causing tissue damage. This finding is in accord with that of Lipsky *et al.* (1980) [38], who also reported similar results. In case of liver, hepatocytes are hexagonal liver cell that contains many metabolic enzymes. Liver damage may exert to pour these enzymes into plasma/serum and can be useful for the determination of liver damage. Urine analysis did not show presence of any bile salt, ketone body, albumin, RBC, caste and crystal (Table 3) during experimental period after intravenous administration in healthy goats. The use of amikacin is responsible for increased production of reactive oxygen species (ROS) associated with an increase in lipid peroxidation which takes place in the cell membranes or tissues. Lipid peroxidation is an oxidative stress which increased the production of ROS and decreased antioxidants which lead to an imbalance between oxidant and antioxidant status and ultimately leading to cellular damage (Nayma *et*

*al.*, 2012; Masakazu *et al.*, 2014) [28, 39]. It is therefore expedient to advise that caution should be exercised in the use of aminoglycoside antibiotics.

**Table 1:** Comparative haematological values after intravenous administration of amikacin in healthy goats

Parameter	0 day	2 <sup>nd</sup> Day	4 <sup>th</sup> Day	6 <sup>th</sup> day
Hb (g.dl <sup>-1</sup> )	10.31±0.12	10.30±0.08	10.32±0.03	10.29±0.06
PCV (%)	32.75±0.47	33.00±0.57	33.00±0.57	33.00±0.40
TEC (10 <sup>6</sup> .µl <sup>-1</sup> )	12.00±0.99	11.75±0.95	11.00±0.93	11.50±0.96
TLC (10 <sup>3</sup> .µl <sup>-1</sup> )	8.65±0.70	8.81±0.73	9.03±0.38	8.78±0.66
Lymphocytes (%)	55.00±1.08	55.25±1.65	53.25±1.31	54.25±1.65
Monocytes (%)	1.00±0.40	1.00±0.40	1.00±0.40	0.75±0.25
Eosinophils (%)	1.00±0.40	1.50±0.28	0.75±0.25	1.00±0.40
Basophil (%)	0.25±0.25	0.25±0.25	0.50±0.28	0.50±0.28
Neutrophils (%)	40.50±0.95	40.50±0.64	41.50±0.28	41.75±0.25

Values are expressed as mean ± SE of four animals in each group

**Table 2:** Comparative serum biochemical values after intravenous administration of amikacin in healthy goats

Parameter	0 day	2 <sup>nd</sup> Day	4 <sup>th</sup> Day	6 <sup>th</sup> day
Albumin (g.dl <sup>-1</sup> )	3.94±0.12	3.88±0.12	3.84±0.11	3.85±0.11
Globulin (g.dl <sup>-1</sup> )	3.94±0.12	3.88±0.12	3.84±0.11	3.85±0.11
Total Protein (mg.dl <sup>-1</sup> )	6.68±0.06	6.71±0.06	6.75±0.06	6.73±0.06
BUN (g.dl <sup>-1</sup> )	18.75±0.25 <sup>a</sup>	19.50±0.29 <sup>a</sup>	21.50±0.29 <sup>b</sup>	21.50±0.50 <sup>b</sup>
Creatinine (mg.dl <sup>-1</sup> )	1.24±0.024 <sup>a</sup>	1.23±0.0122 <sup>a</sup>	1.27±0.085 <sup>ab</sup>	1.30±0.041 <sup>b</sup>
Total bilirubin (mg.dl <sup>-1</sup> )	0.44±0.015	0.45±0.019	0.45±0.019	0.44±0.018
Cholesterol (mg.dl <sup>-1</sup> )	47.25±3.68	48.50±3.52	50.00±3.69	49.00±6.58
Triglyceride(mg.dl <sup>-1</sup> )	38.00±1.29	39.75±1.75	42.00±1.70	39.25±1.93
ALT/GPT (IU.L <sup>-1</sup> )	26.50±1.32 <sup>a</sup>	26.75±1.03 <sup>a</sup>	30.50±1.86 <sup>ab</sup>	34.75±1.31 <sup>b</sup>
AST/GOT (IU.L <sup>-1</sup> )	62.50±3.22 <sup>a</sup>	63.50±2.72 <sup>a</sup>	69.50±1.84 <sup>ab</sup>	71.75±1.65 <sup>b</sup>
ALP (IU.L <sup>-1</sup> )	165.00±5.45 <sup>a</sup>	170.00±6.45 <sup>ab</sup>	177.50±3.22 <sup>ab</sup>	185.00±5.40 <sup>b</sup>

Values are expressed as mean ± SE of four animals in each group

Values bearing different superscript in small letter differ significantly in row respectively (p<0.05).

**Table 3:** Comparative Urine analysis after intravenous administration of amikacin in healthy goats

Parameters	0 day	2 <sup>nd</sup> day	4 <sup>th</sup> day	6 <sup>th</sup> day
Bile salt	Nil	Nil	Nil	Nil
Ketone body	Nil	Nil	Nil	Nil
Albumin	Nil	Nil	Nil	Nil
RBC	Nil	Nil	Nil	Nil
Caste	Nil	Nil	Nil	Nil
Crystal	Nil	Nil	Nil	Nil

## Conclusion

Our present study clarified that treatment with amikacin at therapeutic dose in goats did not show any degree of reduced food and water intake and other behavioral changes. It induced significant increase of serum enzyme level and blood urea and creatinine, whereas did not show any significant changes in other haematological and other serum biochemical parameters and it may cause derangement of liver and kidney function. The present study suggests that we should have to be conscious about taking or prescribing aminoglycoside antibiotic in major or minor issues.

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