

## Renal Wasting of Electrolytes: Effect of Amikacin Used to Treat Infections - Tip of Iceberg for the Physicians

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### ABSTRACT

**Objective:** To measure prospectively the effect of treatment with the Amikacin on renal magnesium, potassium and phosphate wasting in patients with extrarenal infections.

**Study Design:** Case series.

**Place and Duration of Study:** Department of Nephrology, Pak Emirates Military Hospital, Rawalpindi Pakistan from Jul to Dec 2019.

**Methodology:** A total of 40 cases were included in this study in liaison with other departments who were put on Amikacin standard dose. Urinary electrolytes including potassium, magnesium and phosphate were measured at day 4 after the use of Amikacin. Factors like age, gender, cause for which Amikacin was used, day 1 creatinine and day 4 creatinine were correlated with presence of electrolyte wasting in the target population.

**Results:** Mean age of study participants was  $39.1 \pm 12.56$  years. 25(62.5%) were males while 15(37.5%) were females. Commonest cause for the use of Amikacin was drug resistant tuberculosis followed by fractures. Mean urinary magnesium was  $39.1 \pm 12.56$  mmol/24 hours, while potassium was  $26.1 \pm 15.60$  meq/24 hours. Mean phosphate was  $66.4 \pm 53.55$  mg/24 hours. Pearson chi-square test revealed that advanced age and day 4 creatinine were strongly linked with the presence of urinary electrolyte wasting among the patients receiving Amikacin for extra-renal infections with  $p$ -value < 0.05.

**Conclusion:** Electrolyte wasting emerged as a common finding in the patients put on Amikacin suffering from extra renal infections. Patients with advancing age put on Amikacin should be given special attention and screened for electrolyte wasting at priority. Day 4 creatinine levels could be incorporated in routine screening to have an idea regarding electrolyte wasting or renal damage.

**Keywords:** Amikacin, Electrolyte wasting, Infections.

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### INTRODUCTION

Infectious diseases make a surfeit of all the diseases from which mankind suffers in all parts of the world.<sup>1</sup> Various antibiotics have been in clinical practice to combat the bacterial infections. Aminoglycosides have been a considerable class of antibiotics for long and had been more often deployed against the gram negative bacteria which frequently cause debilitating infections.<sup>2</sup> Despite their effectiveness; they might inclined the sufferers towards some untoward effects which need to be addressed. Ototoxicity and nephrotoxicity have been two familiar and critical facet consequences which arises after the use of aminoglycosides.<sup>3</sup>

Various electrolytes have been necessary for the cohesion of important functions of human body. Sodium, potassium, magnesium, calcium, chloride and phosphate have been few paramount electrolytes in human body of which sodium and potassium exten-

sively studied but less precedence on magnesium and phosphate which are equally important.<sup>4</sup> Many medical conditions may meddle with excretion of these electrolytes and lead to wasting or toxicity.<sup>5</sup> Renal damage due to various pharmacological agents may be one of the causes of electrolyte imbalance.<sup>6,7</sup>

Serum electrolytes vacillate usually when long term or severe renal damage exist. Short term changes are usually fended by compensatory mechanisms so urinary electrolyte measurement have been used to look for early detection of the electrolytes loss. Elliot *et al.* concluded that gentamicin caused renal calcium and magnesium wasting in human beings without any illness. The mechanism of gentamicin-associated urinary magnesium and calcium wasting could not be inferred clearly, however, distal convoluted tubule has been the proposed site for this wasting of important electrolytes.<sup>8</sup> Another study done in Switzerland revealed that Amikacin was responsible for urinary wasting of magnesium leading to significant hypomagnesaemia among the pediatric population.<sup>9</sup> Even neonates showed this apparitions and serum urea and

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creatinine levels did not reflect any renal damage but fractional excretion of magnesium was found markedly increased after administration of aminoglycosides. Therefore aminoglycoside induced nephrotoxicity could be screened early by measuring urinary electrolytes in most of cases.<sup>10</sup>

The treating physicians should take cognizance of this effect of aminoglycoside use and screened patients perpetually for this issue. Data from patients of Pakistan has been exiguous in this regard. We therefore concocted this study at our nephrology department in collaboration with the infectious diseases and orthopedic department to measure prospectively the effect of treatment with the Amikacin on renal magnesium, potassium and phosphate wasting in patients with extra renal infections managed at Pak Emirates Military hospital during the study period.

### METHODOLOGY

The case series was conducted for six months from July 2019 to December 2019 at Pak Emirates Military Hospital. Consecutive sampling technique was used to gather the sample from infectious disease and orthopedic department as Amikacin is rarely used now adays so sample size comprised of all the cases reporting in the study period.<sup>11,12</sup>

**Inclusion Criteria:** Patients with extrarenal infection having normal renal function tests and put on aminoglycoside as a primary antibiotic to control the infection were included.

**Exclusion Criteria:** Patients with renal disease or diabetes and patients with blood glucose level >7mmol/l, patients taking diuretic or any other drug causing electrolyte disturbances, patients with interval intake of hospital treatment intake of <3 months, pregnant patients were excluded. Patients put on multiple antibiotics or those with any metastatic or immunological disease were also not included in this study.

Hospital ethical committee granted ethical approval for this study (letter no. 15). Antibiotic Amikacin in a dose of 10-15mg/kg was instituted in all patients as a single daily dose and then adjusted to achieve trough plasma concentration of Amikacin.<sup>11-13</sup> Before and after 04 day blood samples for creatinine, albumin, electrolytes (sodium, potassium, calcium, magnesium, phosphate) taken along with 24 hour urine specimen was collected after overnight fasting for electrolyte analysis (magnesium, potassium, phosphate and creatinine clearance). Age and gender of all patients were noted along with other relevant demographic information on a proforma especially designed for this study. Blood

samples were all done at the Armed Force Institute of Pathology (AFIP) by the same professional. Under aseptic precautions, 5ml of venous blood was drawn from each subject and transferred to a clean, dry test tube to clot. Then the sample was centrifuged and serum was collected in an eppendorf tube and preserved at -200C. Then serum creatinine was measured by using the kinetic method according to the Jaffé method without deproteinisation The urine samples were collected in sterile bottles without any preservatives and the physical, chemical, and microscopic properties of the urine were recorded by general urine analysis then stored at -80°C pending analysis.<sup>14</sup> Wasting of different electrolytes in 24 hour urine taken as standard were, Magnesium >4.3mmol/24hrs, Potassium >30meq/24hrs, Phosphate >100mg/24 hrs.<sup>15</sup>

In the statistical analysis, SPSS for Windows (version 12.0.1) was used. Mean and Standard deviation was calculated for age and duration of Amikacin intake and urinary electrolytes levels for each patient. Frequency of wasting of potassium, magnesium and phosphate was calculated as percentages. Pearson chi-square test was performed to see the effect of age, gender, cause for infection and day 1 and day 4 serum creatinine levels on urinary wasting of electrolytes. The *p*-value for chi-square test was considered significant if it was ≤0.05.

### RESULTS

Forty patients receiving Amikacin in medicine and infectious diseases department were included in the study. Mean age of study participants was 39.1±12.56 years. 25(62.5%) were males while 15(37.5%) were females. Commonest cause for the use of Amikacin was drug resistant tuberculosis followed by osteomyelitis. Mean urinary magnesium was 39.1±12.56 mmol/24hrs, while potassium was 26.1±15.60 mEq/24hrs. Mean phosphate was 66.4±53.55 mg/24hrs.

**Table-I. Characteristics of Patients who received Amikacin (n=40)**

Age (years) Mean±SD	39.1(±12.56)
<b>Gender</b>	
Male	25(62.5%)
Female	15(37.5%)
Mean urinary Potassium	26.1±15.60 mEq/24 hours
Mean urinary Magnesium	39.1±12.56 mmol/24 hours
Mean urinary Phosphate	66.4±53.55 mg/24 hours
Mean day 1 creatinine	87.5±8.26 µmol/L
Mean day 4 creatinine	97.5±11.16 µmol/L
<b>Causes for Amikacin</b>	
Tuberculosis	16(40%)
Osteomyelitis	14(35%)
Septicemia	04(10%)
Urinary tract infection	04(10%)
Others	02(5%)

Mean creatinine at day 1 was  $87.5 \pm 8.26 \mu\text{mol/L}$ , while at day 4 it was  $97 \pm 11.16 \mu\text{mol/L}$ . 29(72.5%) patients had one or more electrolyte wasting while 11(27.5%) patients had all urinary electrolytes in normal range.<sup>15</sup> Pearson chi-square test revealed that advanced age and day 4 creatinine were strongly linked with the presence of urinary electrolyte wasting among the patients receiving Amikacin for extra-renal infections with  $p$ -value  $< 0.05$  (Table-II)

**Table-II: Relationship of Variables with Presence of Electrolyte Wasting (n=40)**

Sociodemographic factors	No Wasting n(%) 11(27.5)	Presence of wasting n(%) 29(72.5)	p-value
<b>Age</b>			
12-45 year	08(72.7%)	04(13.8%)	<0.001
>45	03(27.3%)	25(86.2%)	
<b>Gender</b>			
Male	07(63.6%)	20 (68.9%)	0.748
Female	04(36.4%)	09(31.1%)	
<b>Day 1 Creatinine (<math>\mu\text{mol/L}</math>)</b>			
Within range	11(100%)	25(87.5%)	0.194
Raised	00(00%)	04(12.5%)	
<b>Day 4 Creatinine (<math>\mu\text{mol/L}</math>)</b>			
Within range	10(90.9%)	15(51.7%)	0.022
Raised	01(9.1%)	14(48.3%)	
<b>Cause for Amikacin Use</b>			
Tuberculosis	(63.6%)	09(31.1%)	0.389
Osteomyelitis	02(18.2%)	12(41.3%)	
Septicemia	01(9.1%)	03(10.3%)	
UTI	01(9.1%)	03(10.2%)	
Others	00(00%)	02(6.8%)	

## DISCUSSION

Sound renal functioning has been the requisite for maintaining overall equipoise in the body.<sup>16</sup> Kidneys become strained easily and prone to whittle away early if patient harboring very serious infection. Antibiotics used to treat the infection if nephrotoxic may further add insult to the kidney. Comorbid medical conditions like DM, HTN, IHD or RA may exacerbate the situation as they also have a negative impact on renal function. Therefore, before prescribing the antibiotic these factors should be kept in mind. Previously short course of antibiotics was not considered to be associated with gross effect on kidneys as urea and creatinine were the parameters used to assess the renal function but recently electrolyte wasting has emanated as a new modality to assess the renal functioning after administration of drugs affecting the renal functions especially the antibiotics. We planned this study with the aim to measure prospectively the effect of treatment with the Amikacin on renal magnesium, potassium and phosphate wasting in patients with extra renal infections.

More than seventy percent of our patients showed at least one kind of electrolyte wasting, May it be potassium, magnesium or phosphate. These results were in congruence with the existing literature especially studies done by Vigier *et al.* in 2000 and Alinejad *et al.* in 2018.<sup>9,17</sup> Magnesium was the electrolyte which was most affected by the use of Amikacin and mean magnesium urinary levels in our target population were far greater than the normal range. Studies in the past done by Sonia *et al.* in 2016 and Jan *et al.* in 2017 have corroborated same findings.<sup>10,11</sup> Distal convoluted tubule has been the propounded site for reabsorption of magnesium ions and aminoglycoside thwart with this ,leading to the wasting of this paramount electrolyte,<sup>11</sup> which if incessant for a long period may lead to magnesium deficiency in the body.

Drug resistant tuberculosis was the commonest indication for which Amikacin was used in our target population followed by the patients with osteomyelitis or patients admitted in orthopedic ward with wound infections. These results have been similar to those engendered by studies done in other countries regarding use of aminoglycosides especially study done by Sturkenboom *et al.* in 2018 is important in this regard.<sup>18</sup> It sometimes becomes difficult to distinguish the electrolyte wasting due to underlying infection or medical condition and antibiotic use.

Advancing age was considerably related to presence of electrolyte wasting in our target populace. Literature in the past also conjointly supports our outcomes.<sup>19</sup> It has been clearly incontestable that the renal function ebbs away with the age and both the quirk and quantum of nephrons get impeded. Therefore if the older kidney countenances any insult in form of systemic illness or pharmacological agenize, it is more amenable to damage as compared to a younger kidney especially if confounding factors have been controlled.

The co-relation of electrolyte wasting with serum creatinine at day 4 had been an intriguing finding. This finding has also been seen in the study conducted by Piccoli *et al.* in the recent past.<sup>20</sup> It shows that the renal vandalism with the administration of antimicrobials have been culpable both for raised creatinine and electrolyte wasting. Therefore, creatinine monitoring may be used as a tool where amenity of urinary electrolytes is not accessible and Amikacin administration is requisite. Repeated serum electrolytes levels ought to additionally be carried out as long term wasting may engender decreased levels of these electrolytes in serum leading to momentous sequelae.

Study design poses some concerns relating to generalizability of the results. As baseline electrolytes prior to the administration of Amikacin were not being done so it cannot be inferred from results that electrolyte wasting ensue following Amikacin use. Moreover it could also not be differentiated that electrolyte wasting was a consequence of underlying medical or surgical condition or Amikacin use. Future studies addressing these issues may generate more generalizable results.

### CONCLUSION

Electrolyte wasting brought to light as a common finding in the patients on Amikacin suffering from extra-renal infections. This insight will definitely pave the way for the clinicians to give special attention to patients on Amikacin, especially the elderly populace, and screened for electrolyte wasting at priority. Day 4 creatinine levels and urinary electrolytes should be incorporated in routine screening to have an idea regarding electrolyte wasting or renal damage.

**Conflict of Interest:** None

### Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

BB & KR & IA: Conception, study design, data acquisition, data analysis, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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