

Atorvastatin for Prevention of Amikacin-induced Electrolytes Imbalances; a Randomized Clinical Trial

Behrooz Heydari^a, Hossein Khalili^{a*}, Simin Dashti-Khavidaki^a,
Mohammad Taghi Beig- Mohammadi^b and Mostafa Mohammadi^b

^aDepartment of Clinical Pharmacy, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran. ^bDepartment of Intensive Care Unit, Imam Khomeini Hospital, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran.

Abstract

Aminoglycosides are still widely used for treatment of gram-negative sepsis in critically ill patients. The most reported electrolyte abnormalities related to these drugs are hypokalemia, hypomagnesemia, and hypocalcemia. In this study potential benefit of atorvastatin in prevention of amikacin-induced electrolytes imbalances has been evaluated. In this trial 44 patients were assigned to the atorvastatin or placebo group based on the simple randomization method. Atorvastatin group received amikacin with dose of 15 mg/kg/day in two equal divided doses every 12 h as intravenous infusion during 30 min and atorvastatin 40 mg tablet as daily oral dose for 7 days. Patients in the placebo group received same dose of amikacin and placebo tablet (Placebo group) for at least 7 days. Serum electrolytes (sodium, potassium, calcium, phosphorus and magnesium) concentrations, blood urea nitrogen and serum creatinine levels were measured at day 0 and end of the study. Baseline mean \pm SD of serum potassium concentration in the atorvastatin and placebo group was 4.07 ± 0.37 and 4.15 ± 0.53 meq/l respectively ($p=0.88$). Serum potassium concentration remained unchanged at the end of the study in the atorvastatin group ($P=0.61$) but significantly decreased from 4.15 ± 0.53 to 3.80 ± 0.55 meq/l in the placebo group at day 7 ($P=0.02$). In this pilot study, atorvastatin as 40 mg daily oral dose prevented renal potassium loss during course of amikacin therapy in the critically ill patients. In the future well designed randomized clinical trials with adequate sample size, renoprotective effects of statins should be examined.

Keywords: Amikacin; Atorvastatin; Electrolytes imbalances; Prevention.

Introduction

Infection is a common complication in critically ill patients following hospital admission especially in intensive care unit (ICU). Antibiotics are widely prescribed for control of the patients' infections in this ward. In addition to antibiotic resistant issue, adverse

drug reactions are important concern regarding these drugs. Most adverse effects of antibiotics are mild and reversible but serious ones such as acute kidney injury, acid base disturbances and electrolyte abnormalities can occur in these patients. Acute kidney injury has been reported with many antibiotics, particularly aminoglycosides (AG) and vancomycin. Several mechanisms are proposed for drug-induced acute kidney injury including acute tubular necrosis, allergic acute interstitial nephritis

* Corresponding author:

E-mail: Khaliliah@sina.tums.ac.ir

and vasculitis. Prevention of drug induced kidney injury and consequent electrolytes imbalances can decrease patients' hospitalization costs (1-3). Aminoglycosides are still widely used for treatment of gram-negative sepsis as combination therapy due to their synergistic effects (4). Acute kidney injury is common adverse effect of these drugs (5). Several strategies such as once-daily dosing regimen, correction of volume depletion, hypomagnesaemia or hypokalemia before administration of these drugs and use of nephroprotective agents are proposed to decrease AG-induced nephrotoxicity (6-8). The most reported electrolyte abnormalities related to AG are hypokalemia, hypomagnesemia, and hypocalcemia that are attributed to their renal tubular injury (9). The cationic particles of AG attach to anionic membrane phospholipids, therefore lysosomes swallow with phospholipid material and reduced generating of energy (10). It has been shown that atorvastatin may protect renal tubular cells from free radicals damage induced by gentamicin (4). Intracellular isoprenoid pyrophosphates modified post-translation function of GTP-binding protein receptors. Isoprenoid pyrophosphates are metabolites of mevalonate that are made from the processing of mevalonate by 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase. Multi-ligand receptor megalin is a GTP-binding protein receptor that mediates endocytosis of AG. Atorvastatin inhibits HMG-CoA reductase and may change intracellular isoprenoid pyrophosphates. Atorvastatin reduced AG-renal proximal tubule accumulation and cytotoxicity (11). In this study potential benefit of atorvastatin in prevention of amikacin-induced electrolytes imbalances has been evaluated.

Methods

This double-blinded, randomized clinical trial was conducted in critically ill patients hospitalized in general ICU of Imam Khomeini Hospital affiliated to Tehran University of Medical Sciences, Tehran, Iran, from June 2013 until June 2014. Adult patients (aged between 16-65 years old) who were candidate for AG (Amikacin) therapy for at least 7 days were recruited. Included patients or their caregivers signed the study consent form and the Medical

Ethics Committee of the hospital approved the study. Provided data are part of a RCT results registered in IRCT as IRCT201301283449N11.

Patients with renal impairment (eGFR < 60 ml/min), liver function dysfunction (liver enzyme serum levels over 5 times of the upper limit of normal), history of atorvastatin hypersensitivity reactions, positive history of drug induced myopathy or creatine phosphokinase over 5 times of the upper limit of normal, who received other nephrotoxic drugs or potential nephroprotective agent such as silymarin and vitamin E were excluded from the study.

Recruited patients were assigned to the atorvastatin or placebo group based on the simple randomization method. Atorvastatin group received amikacin with dose of 15 mg/kg/day in two equal divided doses every 12 h as intravenous infusion during 30 min and atorvastatin 40 mg tablet as daily oral dose for 7 days. Patients in the placebo group received same dose of amikacin and placebo tablet (Placebo group) for at least 7 days.

Demographic data (including age, sex, baseline diseases and causes of hospital admission) were extracted from the medical charts and clinical characteristics (such as fever, hemodynamic parameters and type of infections and drug regimens) of the included patients were monitored daily. Serum electrolytes (sodium, potassium, calcium, phosphorus and magnesium) concentrations, blood urea nitrogen and serum creatinine levels were measured at day 0 and end of the study.

Considerable adverse drug reactions of atorvastatin including myopathy and hepatotoxicity were followed by measuring the patients' serum creatine phosphokinase and liver enzyme tests at baseline and end of the study. Increases in serum creatinine (doubling from the baseline value) were considered AG-induced acute kidney injury.

Data were analyzed using SPSS software version 14. Continuous data were expressed as mean \pm standard deviation. Categorical variables were reported as percentages. Chi square or Fisher exact test (if more than 20 % of the categories have expected frequencies less than 5) was used for comparing categorical variables between the groups. Changes in the patients'

Table 1. Descriptive and laboratory parameters of the patients in the atorvastatin and placebo groups.

Variables	Atorvastatin group	Placebo group	P value
Age ,mean \pm SD	59 \pm 19	49 \pm 18	0.074
Gender (n)			
❖ Male	12	14	
❖ Female	7	11	0.632
APACHE II, mean \pm SD	20.3 \pm 5.3	19.7 \pm 4.4	0.684
Mortality (n)	5	4	0.401
Chronic disease (n)			
❖ Respiratory Diseases	2	2	
❖ Cancer	1	2	
❖ Cardiovascular diseases	16	12	
❖ Neurological diseases	1	2	
❖ Diabetes	5	0	
❖ Hypothyroidism	2	1	
❖ Total	37	19	0.083
Admission Diagnoses (n)			
❖ Cancer	8	8	0.49
❖ Respiratory failure	4	0	0.016
❖ Cardiac problems	2	1	0.395
❖ Neurological disorders	1	1	0.842
❖ Trauma	2	6	0.395
❖ Abdominal complications	2	6	0.395
❖ Orthopedic surgeries'	0	3	0.067
complications			
Culture results of the patients' biological samples(n)			
❖ Negative	8	17	0.086
❖ Respiratory	8	4	0.054
❖ Blood	1	1	0.842
❖ Urine	0	2	0.207
❖ Wound	1	1	0.842
Microorganism (n)			
❖ Acinetobacter	2	4	0.6
❖ Enterobacter	2	0	0.097
❖ Pseudomonas	4	0	0.016
❖ Klebsiella	3	3	0.717
❖ Streptococcus viridians	0	1	0.378
Hemoglobin concentration (g/dl)			
❖ Before treatment	9.77	9.72	0.924
❖ After treatment	9.86	9.66	0.698
Platelet count (cells/mm ³)			
❖ Before treatment	239 \pm 134	251 \pm 159	0.792
❖ After treatment	320 \pm 188	288 \pm 168	0.561
INR			

Table 1. (Continued).

❖ Before treatment	1.25 ± 0.47	1.36 ± 0.53	0.473
❖ After treatment	1.23 ± 0.35	1.26 ± 0.26	0.758
pH			
❖ Before treatment	7.42 ± 0.06	7.4 ± 0.08	0.185
❖ After treatment	7.42 ± 0.07	7.44 ± 0.05	0.452
HCO ₃ (meq/l)			
❖ Before treatment	24.8 ± 3.5	24.9 ± 6.3	0.944
❖ After treatment	25.5 ± 4.4	25.5 ± 5.1	0.996
Pco ₂ (mmHg)			
❖ Before treatment	40.4 ± 6.05	40.8 ± 10.6	0.89
❖ After treatment	41.75 ± 8.13	38.7 ± 9.77	0.275
Sodium intake (mEq/day)	413.4 ± 103.3	400.4 ± 117.6	0.705
Potassium intake (mEq/day)	24.2 ± 18.75	21.7 ± 19.7	0.674
Calcium intake (mEq/day)	15.79 ± 40.4	24.4 ± 39.8	0.484
Phosphor intake (mmol/day)	1.16 ± 2.77	1.84 ± 5.56	0.627
Magnesium intake (mEq/day)	5.3 ± 13.37	14.88 ± 22.6	0.088
Antibiotic Regimens			
❖ Vancomycin + Carbapenem + Amikacin	10	15	
❖ Vancomycin + Tazocin + Amikacin	0	2	
❖ Vancomycin + Cephalosporins + Amikacin	1	2	
❖ Vancomycin + Amikacin	1	0	
❖ Carbapenem + Amikacin	4	4	
❖ Tazocin + Amikacin	3	1	
❖ Carbapenem + Metronidazole + Amikacin	0	1	
TOTAL	19	25	0.467
Indications of amikacin administration			
❖ Respiratory	17	16	
❖ Sepsis	2	8	
❖ Peritonitis	0	1	
Total	19	25	0.143
Other Drugs			
❖ PPI	14	21	0.401
❖ Ranitidine	5	4	0.401
❖ Diuretics	4	3	0.416
❖ Hydrocortisone	2	2	0.773
❖ Vancomycin	12	19	0.355
❖ Carbapenems	14	20	0.62
❖ Tazocin	3	3	0.717
❖ Cephalosporins	1	2	0.721
❖ Inotropic agents	4	8	0.419

Table 1. (Continued).

Metabolic support			
❖ Parenteral nutrition	2	6	
❖ Enteral nutrition	12	13	
❖ Oral intake	1	2	
❖ Parenteral and enteral nutrition	4	4	
Total	19	25	0.663
Fluid balance			
❖ Input	3.3 ± 0.59	3.4 ± 0.52	0.686
❖ output	2.6 ± 0.5	2.7 ± 0.48	0.699
Liver function tests			
❖ AST (IU/L)	40.79 ± 20	55.6 ± 40.4	0.152
❖ ALT (IU/L)	37.5 ± 20.8	54.96 ± 48.87	0.118
Muscle injury assessment			
❖ CPK (mcg/L)	33.18 ± 9.47	28.95 ± 16.87	0.371

serum electrolytes (sodium, calcium, potassium, magnesium and phosphor) concentrations, blood urea nitrogen and serum creatinine before and after the intervention were compared using paired sample t-test. Independent sample t-test was used to compare changes in the serum electrolytes between two groups of the study.

Results

In the initial screening of the hospitalized patients in the general ICU, during one-year period, 61 patients met inclusion criteria of the study. During the study period, seventeen patients were excluded due to discharge from the ward (10 patients), death (4 patients) and discontinuation of amikacin (3 patients). Finally 44 patients (19 patients in the atorvastatin group and 25 patients in the placebo group) completed the study (Figure 1). The patients mean ± SD of age in the atorvastatin and placebo groups was 59 ± 18 and 49 ± 19 years respectively ($p=0.07$). There was no significant difference in the patients sex between the groups ($p=0.63$). The patients' severity of the diseases based on the APACHE score II (acute physiologic and chronic health evaluation) was not different at the admission time ($p=0.68$). The patients' types of the baseline diseases and diagnosis at the admission time were comparable. Cultures of

the biological samples (blood, urine, respiratory tract secretions or wound) were positive in 11 (57.89%) and 8 (32.00%) of the patients in the atorvastatin and placebo group respectively. *Acinetobacter spp.* (31.57%), *Klebsiella spp.* (31.57%), *Pseudomonas aeruginosa* (21.05%) and *Enterobacter spp.* (10.52%) were the most common isolated microorganisms. Respiratory tract infections (mostly ventilator associated pneumonia (75.00%), sepsis (22.72%) and peritonitis (2.28%) were indications for amikacin administration in There was not any significant difference between the groups regarding the patients' common laboratory data including hematologic parameters. Descriptive characteristics and laboratory parameters of the patients are summarized in the table 1.

Regarding the patients' renal function during the study period, there was no significant change in the blood urea nitrogen (BUN) and serum creatinine before and after the intervention in the both groups.

At baseline, before initiation of the intervention, mean ± SD of the patients' serum sodium concentration was 138 ± 5.52 and 136 ± 4.29 meq/L in the atorvastatin and placebo group respectively ($p=0.95$). In the both groups, serum sodium did not change before and after treatment significantly ($P>0.05$). Also difference between serum sodium concentration at the end of the

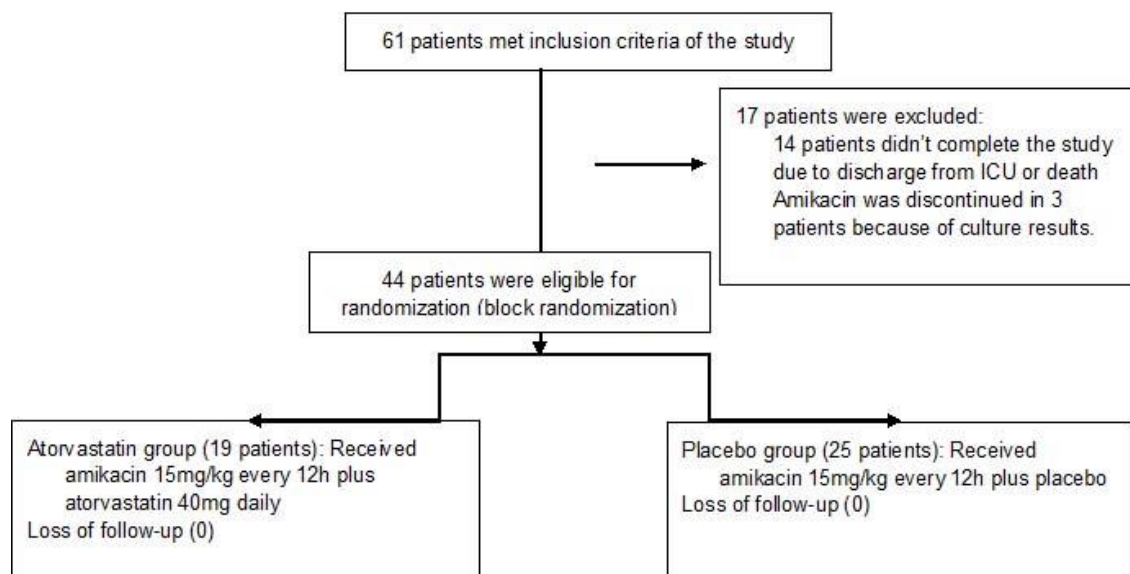


Figure 1. Consort flowchart of the study.

study remained insignificant between the groups ($P = 0.56$).

Baseline mean \pm SD of serum potassium concentration in the atorvastatin and placebo group was 4.07 ± 0.37 and 4.15 ± 0.53 meq/L respectively ($p = 0.88$). Serum potassium concentration remained unchanged at the end of the study in the atorvastatin group ($P = 0.61$) but significantly decreased from 4.15 ± 0.53 to 3.80 ± 0.55 meq/L in the placebo group at day 7 ($P = 0.02$). However, difference of the serum potassium concentration at the end of the study was insignificant between the groups.

The patients' serum calcium, magnesium and phosphorus concentrations did not differ between the groups at the baseline and day 7 of the study. Also, changes in the concentrations of these electrolytes were not significant within each group during the study period. The serum electrolyte concentrations of the included patients are summarized in table 2.

Discussion

Intra- and extracellular concentrations of electrolytes are necessary for many metabolic processes and maintenance of the normal organ functions (12). Electrolyte imbalances are common in critically ill patients. Several

complications such as respiratory failure, edema, muscle weakness, altered mental status, and arrhythmias have been reported following electrolyte imbalances in the patients hospitalized in ICU (12).

Normal function of most vital organs, especially kidney, are necessary for the human body electrolyte regulation (13). In addition to the body organ dysfunction, electrolyte imbalances could be a consequence of administration of some medications such as AG antibiotics. Electrolyte imbalances are associated with renal toxicity of AG (14-15). These drugs accumulate in the epithelial cells in the renal cortex, mainly in the proximal and distal tubules and collecting ducts. Aminoglycosides enter the mentioned cell by endocytosis through a transporter of proteins and cations called megalin and cubilin (15-16). After influx, they accumulate mostly in lysosomes, the Golgi, and endoplasmic reticulum. When the concentration of AG in the endosomal systems exceeds, their membrane is disrupted and their contents are released into the cytosol. Cytosolic AG acts on mitochondria and stimulates the intrinsic pathway of apoptosis, interfering with the cell's respiratory chain and reducing ATP production, which further causes cell death (18). Electrolyte imbalances associated with AG consisted of hypokalemia, hypomagnesemia,

Table 2. Changes in the serum electrolytes concentrations in the atorvastatin and placebo groups.

Electrolyte	Atorvastatin group		Placebo group	
	At baseline	After treatment	At baseline	After treatment
Serum sodium concentration (mEq/L)	138 ± 5.52	135.8 ± 4.60	136 ± 4.29	136.6 ± 6.50
P value		0.096		0.719
Serum potassium concentration (mEq/L)	4.07 ± 0.37	4.17 ± 0.63	4.15 ± 0.53	3.80 ± 0.55
P value		0.61		0.02
Serum calcium concentration (mg/dL)	7.5 ± 1.01	7.66 ± 0.88	7.4 ± 0.48	7.8 ± 0.82
P value		0.352		0.23
Serum phosphor concentration (mg/dL)	2.94 ± 0.39	3.36 ± 0.59	2.96 ± 0.52	3.45 ± 0.4
P value		0.074		0.021
Serum magnesium concentration (mg/dL)	2.2 ± 0.26	2.3 ± 0.44	1.86 ± 0.31	2.06 ± 0.29
P value		0.423		0.094
Serum creatinine concentration (mg/dL)	0.76 ± 0.2	0.76 ± 0.2	0.76 ± 0.3	0.76 ± 0.3
P value		1		0.94
BUN concentration (mg/dL)	36.1 ± 15.4	40.1 ± 26.5	36.4 ± 20.5	39.2 ± 23.5
P value		0.494		0.57

and hypocalcemia. The exact mechanisms of AG-induced electrolyte abnormalities are unknown. It seems renal tubular chloride channel may stimulate by AG resulting in excessive urinary chloride loss. Following sodium chloride wasting, renin-angiotensin-axis is stimulated and subsequently hypokalemic metabolic alkalosis occurs. Hypokalemia may induce hypomagnesemia (1). In addition, AG can decrease brush border membrane enzymes and phospholipids and consequently decrease transport of organic bases, electrolytes (sodium, potassium and calcium) and also decrease of Na-KATPase activity (15).

Intracellular isoprenoid pyrophosphates modified post-translation function of GTP-binding protein receptors. Isoprenoid pyrophosphates are metabolites of mevalonate that are made from the processing of mevalonate by 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase. Multi-ligand receptor megalin is a GTP-binding protein receptor that mediates endocytosis of AG. Atorvastatin inhibits HMG-CoA reductase and consequently changes intracellular isoprenoid pyrophosphates.

Based on this mechanism, atorvastatin results in reduction in AG renal proximal tubule accumulation and cytotoxicity (11). In 2009, Emin Ozbek *et al.* study results showed that atorvastatin may protect kidney of rats from free radicals induced by gentamicin (4).

Renal toxicity was not detected in any patient in the both groups. Serum potassium concentration remained unchanged after treatment in the atorvastatin group but was decreased in the placebo group following 7 days of amikacin therapy. Hypokalemia is reported as the most common type of electrolyte imbalances following AG therapy (17-20).

Small sample size and short duration of the patients' follow-up are the major limitation of this study. Also we did not measure urine electrolytes and effects of AG and atorvastatin on the urinary electrolytes loss.

Present study is first human randomized clinical trial that has evaluated possible effects of atorvastatin in prevention of AG-induced electrolyte imbalances. During a 7-day course of amikacin therapy we did not detect any renal adverse effects including acute kidney injury or

electrolytes imbalances except decreasing serum potassium concentration. In this pilot study, atorvastatin as 40 mg daily oral dose prevented renal potassium loss during course of amikacin therapy in the critically ill patients. In the future well designed randomized clinical trials with adequate sample size and longer duration of patients' follow-up, renoprotective effects of statins should be examined.

Reference

- (1) Kim YW. Antimicrobial-induced electrolyte and acid-base disturbances. *Electrolyte. Blood. Press.* (2007) 5: 111-115.
- (2) Khalili H, Soltani R, Negahban S, Abdollahi A and Gholami K. Reliability of Disk Diffusion Test Results for the Antimicrobial Susceptibility Testing of Nosocomial Gram-positive Microorganisms: Is E-test Method Better?. *Iran. J. Pharm. Res.* (2012) 11: 559-63.
- (3) Khalili H, Sheikhababayi M, Samadi N, Jamalifar H, Dalili D and Samadi N.
- (4) Bacterial contamination of single- and multiple-dose vials after multiple use and intravenous admixtures in three different hospitals in iran. *Iran. J. Pharm. Res.* (2013) 12: 205-9.
- (5) Ozbek E, Cekmen M, Ilbey YO, Simsek A, Polat EC and Somay A. Atorvastatin prevents gentamicin-induced renal damage in rats through the inhibition of p38-MAPK and NF-kappaB pathways. *Ren. Fail.* (2009) 3: 382-92.
- (6) Asif AH, Rasool ST and Khan TM. Pyridoxal phosphate a possible intervention to prevent aminoglycoside induced electrolyte imbalance. *J. Clin. Res. Bioeth.* (2012) 3: 124.
- (7) Sandhu JS, Sehgal A, Gupta O and Singh A. Aminoglycoside nephrotoxicity revisited. *J. Ind. Acad. Clin. Med.* (2007) 8: 331-3.
- (8) Freeman CD, Nicolau DP, Belliveau PP and Nightingale CH. Once-daily dosing of aminoglycosides: review and recommendations for clinical practice. *J. Antimicrob. Chemother.* (1997) 39: 677-686.
- (9) Prins JM, Weverling GJ, de Blok K, van Ketel RJ and Speelman P. Validation and nephrotoxicity of a simplified once-daily aminoglycoside dosing schedule and guidelines for monitoring therapy. *Antimicrob. Agents Chemother.* (1996) 40: 2494-2499.
- (10) Elliott C, Newman N and Madan A. Gentamicin effects on urinary electrolyte excretion in healthy subjects. *Clin. Pharmacol. Ther.* (2000) 67: 16-21.
- (11) Kang HS, Kerstan D, Dai L, Ritchie G and Quamme GA. Aminoglycosides inhibit hormone-stimulated Mg²⁺ uptake in mouse distal convoluted tubule cells. *Can. J. Physiol. Pharmacol.* (2000) 78: 595-602.
- (12) Antoine DJ, Srivastava A, Pirmohamed M and Park BK. Statins inhibit aminoglycoside accumulation and cytotoxicity to renal proximal tubule cells. *Biochem. Pharmacol.* (2009) 79: 647-654.
- (13) Buckley MS, LeBlanc JM and Cawley MJ. Electrolyte disturbances associated with commonly prescribed medications in the intensive care unit. *Crit. Care Med.* (2010) 38: S253-264.
- (14) Kasama R and Sorbello A. Renal and electrolyte complications associated with antibiotic therapy. *Am. Fam. Physician* (1996) 53: 227-32.
- (15) Humes HD. Aminoglycoside nephrotoxicity. *Kidney. Int.* (1988) 33: 900.
- (16) Zietse R, Zoutendijk R and Hoorn EJ. Fluid, electrolyte and acid-base disorders associated with antibiotic therapy. *Nat. Rev. Nephrol.* (2009) 5: 193-202.
- (17) Lopez-Novoa JM, Quiros Y, Vicente L, Morales AI and Lopez-Hernandez FJ. New insights into the mechanism of aminoglycoside nephrotoxicity: an integrative point of view. *Kidney. Int.* (2011) 79: 33-45.
- (18) Chou CL, Chen YH, Chau T and Lin SH. Acquired bartter-like syndrome associated with gentamicin administration. *Am. J. Med. Sci.* (2005) 329: 144-9.
- (19) Ray PE, Suga S, Liu XH, Huang X and Johnson RJ. Chronic potassium depletion induces renal injury, salt sensitivity, and hypertension in young rats. *Kidney Int.* (2001) 59: 1850-8.
- (20) Elliott C, Newman N and Madan A. Gentamicin effects on urinary electrolyte excretion in healthy subjects. *Clin. Pharmacol. Ther.* (2000) 67: 16-21.
- (21) Liamis G, Milionis HJ and Elisaf M. A review of drug-induced hypocalcemia. *J. Bone Miner. Metab.* (2009) 27: 635-642.

This article is available online at <http://www.ijpr.ir>