ORIGINAL ARTICLE

Electrolyte Imbalance Associated with Aminoglycosides - An Experimental study

MUHAMMAD ZAHID[1], SHAKEEL AHMED[2], SHAHZAD ANJUM[3]

ABSTRACT

Aim: To evaluate the electrolyte imbalance associated with the use of two important Aminoglycosides (Amikacin and Gentamicin) in experimental rabbit model. Gentamicin and Amikacin 5mg/kg/day and 15mg/kg/day respectively were continued for seven days in two different groups i.e., Group G (Gentamicin treated group) and Group A (Amikacin treated group) along with Control Group (Group C) being on simple isotonic saline for the same period. Blood samples from ear veins were collected at 0 (before therapy), 3rd and 7th day and analyzed for BUN, Serum Creatinine, Sodium, Potassium and Calcium. Biostatistical analysis at the end of the study showed that there was a significant decrease in serum sodium, potassium and calcium levels in both Gentamicin and Amikacin groups when compared with control group. There was no significant change in blood urea nitrogen (BUN) and serum creatinine before and after the treatment for 07 days. So it is concluded that serum electrolytes should be monitored while treating the patients with Aminoglycosides and other antibiotics and corrective measures should be adopted accordingly. Patients who are prone to electrolyte imbalance should be observed carefully by the healthcare providers to manage the patients more efficiently.
Keywords: Aminoglycosides, Electrolyte imbalance

INTRODUCTION

Aminoglycosides are still the mainstay in the antimicrobial therapy, since their introduction about more than 50 years ago[1]. They are still used against Gram positive and Gram negative bacterial pathogens in antimicrobial combinations[2-3] and display highly desirable properties like concentration dependent effects[4] and post antibiotic effects[5]. Despite the emergence of advanced pattern of antimicrobial resistance in Gram negative strains, physicians prompt to use these old antimicrobial agents due to their low incidence of resistance[6]. Their efficacy continues to be counterbalanced by significant toxicities. It has been observed that certain drugs cause approximately 20% of community and hospital acquired episodes of acute renal failure.

The use of antibiotics including Aminoglycosides can cause fluid, electrolytes and acid base disorders. The antibiotics affect at various sites on renal tubules e.g., Aminoglycosides and tetracyclines cause dysfunction of proximal tubules also known as Fanconi's Syndrome. Besides aminoglycosides also act on the loop of Henle and cause Bartter like syndrome. Collecting ducts may also be involved thus, leading to derangements in electrolyte balance and nephrogenic diabetes inspidus[7].

[1,3]Department of Pharmacology and Therapeutics, [2]Department of Biochemistry, K. E. M. U. Lahore.
Correspondence to Dr. Muhammad Zahid, Head of Department Email: drzahidpharma@hotmail.com Cell: 0322-4414027

In our present study we shall evaluate the effects of aminoglycosides i.e., Amikacin and Gentamicin on serum electrolytes, blood urea nitrogen and serum creatinine at normal clinical doses.

MATERIALS AND METHODS

The study was conducted on rabbits of local breed. A total of 18 male rabbits, weighing 1 to 1.75kg and age ranging from 8 to 10 months were included and housed for 14 days at Postgraduate Medical Institute, Lahore for acclimatization. The biologic clock (twelve hours light and dark cycle) was maintained. The rabbits were fed on commercial diet and had water ad libitum. Following aminiglycoside preparations commercialized for clinical application were used for the current study:

1. Injection amikin containing 250mg of amikacin sulphate in 2ml solution prepared by Bristol-myera/Squibb.
2. Injection Genticin containing 80mg of gentamicin sulphate in 2ml solution prepared and contained a mixture of three main components, gentamicin C1, C2 and C3.

The rabbits were divided into three groups at random with 6 animals in each. All the drugs were administered through intramuscular route. The solution for evening dosages was stored in refrigerator. All the agents were given at twelve hour interval (8 a.m. and 8 p.m.) for a period of 07 days according to following dosage regimen.

Group C (Control Group): Received 2ml of isotonic saline intramuscularly twice a day.

Group G (Group Gentamicin): Received gentamicin sulphate 5mg/kg/day intramuscularly in two equal divided doses.

Group A (Group Amikacin): Received amikacin sulphate 15mg/kg/day intramuscularly in two equally divided doses.

Collection of Samples: Blood samples were collected for three times during the study i.e. on day 0, day 03 and day 07. Animals were also weighed at the same time.

Blood: blood was collected from the marginal vessels of the ear. For this purpose hair were shaved from the ear margin. It was then disinfected with 70% alcohol. Xylene was applied for vasodilatation. Eight milliliters of blood was drawn from the vein in a centrifuge tube. The bleeding vessel was pressed with a sterilized cotton swab till stoppage of bleeding. The collected blood was allowed to clot at room temperature and then centrifuged at 3000 rpm for ten minutes. Serum was separated with the help of an automatic micropipette and stored in a clean and dry serum storage vial in a deep freezer for estimation of blood urea nitrogen, serum creatinine and electrolytes (Sodium, potassium and calcium).

Data were analyzed using SPSS software version 20. The changes in serum electrolytes (sodium, calcium and potassium) concentrations, blood urea nitrogen and serum creatinine were estimated before and after therapy with Gentamicin and Amikacin in each group were compared by paired t-test. Independent sample t-test was used to compare changes in serum electrolytes between two regimens of therapy. Blood urea nitrogen and serum creatinine levels were also compared at the start, midpoint and at the end of the treatment.

RESULTS

Serum sodium remained statistically unchanged on day 03 in all the groups. However it declined in group G (P<0.05) and in group A (P<0.05) on day 07 as compared with control group (Table 1 and 2). A significant fall in serum levels of potassium was exhibited by the animals of group G (4.11± 0.10 vs. control 5.18±0.15 mEq/L, P<0.001) and group A (4.11±0.15 mEq/L, P<0.001) on day 03. The level of significance between the values of these two groups was maintained on day 07 as well. The largest individual fall in serum potassium in Group G was upto 3.25 mEq/L and in Group A was 3.63 mEq/L (Table 1 and 2). Serum calcium was found significantly decreased in Group G (8.26±0.15 vs. control 9.83±.17 mg/dl, P<0.005 and in Group A (8.86±0.15, P<0.005) on day 03 of the study. This downward trend of serum calcium persisted in both the groups on day 07 as well (Table 1 and 2). However the difference between group G and A was not statistically significant (Table 3).

There was no statistically significant difference in blood urea nitrogen and serum creatinine levels before and after the treatment in control group (Group C) and treatment groups of Gentamicin and Amikacin (Group G and Group A) respectively (Table 4).

Table 1 Effect of Gentamicin (Group G) on Serum Electrolyte Levels

Tests	**Day 0**		**Day 03**		**Day 07**	
	C	**G**	**C**	**G**	**C**	**G**
Serum Sodium(mEq/L)	140.5±0.08	141.5±0.76	139.7±1.12	139.5±0.76	140.02±0.83	137.8±0.56
			N.S		P<0.05	
Serum Potassium(mEq/L)	5.31±0.17	5.11±0.22	5.18±0.15	4.03±0.1	5.06±0.1	3.25± 0.11
			P<0.001		P<0.001	
Serum Calcium (mg/dl)	10.06±0.18	10.27±0.25	9.83±0.17	8.26±0.15	9.65±0.21	7.51±0.15
			P<0.005		P<0.005	

Key: Control Group (C), Gentamicin Group (G), Result Represent mean ± SEM

Table 2 Effect of Akikacin (Group A) on Serum Electrolyte Levels

Tests	**Day 0**		**Day 03**		**Day 07**	
	C	**A**	**C**	**A**	**C**	**A**
Serum Sodium (mEq/L)	140.5±0.08	141.3±1.05	139.7±1.12	139.3±0.88	140.02±0.83	137.6±0.67
			N.S		P<0.05	
Serum Potassium (mEq/L)	5.31±0.17	5.1±0.8	5.18±0.15	4.11±0.15	5.06±0.1	3.63±0.16
			P<0.01		P<0.001	
Serum Calcium (mg/dl)	10.06±0.18	10.3±0.21	9.83±0.17	8.68±0.15	9.65±0.21	7.85±0.15
			P<0.005		P<0.001	

Key: Control Group (C), Amikacin Group (A), Result Represent mean ± SEM

Table 3 Comparison between Gentamicin (Group G) and Amikacin (Group A) on Serum Electrolyte Levels

Tests	Day 0			Day 03			Day 07		
	C	A	G	C	A	G	C	A	G
Serum Sodium (mEq/L)	140.5± 0.08	141.3± 1.05	141.5± 0.76	139.7± 1.12	139.3± 0.88	139.5± 0.76	140.02± 0.83	137.6± 0.67	137.8±0.56
					N.S			N.S	
Serum Potassium(mEq/L)	5.31±0.17	5.1±0.8	5.11±0.22	5.18±0.15	4.11±0.15	4.03±0.1	5.06±0.1	3.63±0.16	3.25±0.11
					N.S			N.S	
Serum Calcium (mg/dl)	10.06±0.18	10.3±0.21	10.27±0.25	9.83±0.17	8.68±0.15	8.26±0.15	9.65±0.21	7.85±0.15	7.51±0.15
					P<0.005			N.S	

Key: Control Group (C), Amikacin Group (A), Gentamicin Group (G), Result Represent mean ± SEM

Table 4 Blood Urea Nitrogen and Serum Creatinine Levels

Tests	Day 0			Day 03			Day 07		
	C	A	G	C	A	G	C	A	G
BUN (mg/dl)	9.2±0.51	10.25±1.12	9.08±0.53	10.73±0.26	10.05±0.63	9.0±0.86	14.26±0.46	9.58±1.19	9.56±0.49
		N.S			N.S			N.S	
Serum Creatinine (mg/dl)	0.433±0.06	0.638±0.79	0.053±0.11	0.73±0.04	0.581±0.08	0.568±0.10	0.94±0.04	0.795±0.04	0.705±1.10

DISCUSSION

Electrolyte balance is essential for the normal function of our body. Electrolyte imbalance can cause a change in amount of water in our body, pH and changes in muscle function[14]. Electrolytes are minerals which become ions in solution and are found in our blood and other body fluids[15].

Electrolyte imbalance could be caused by inadequate intake, malabsorption, endocrine disorders, kidney diseases and by some antibiotics. Aminoglycosides also cause electrolyte imbalance and contribute to derangements of renal functions by accumulating on brush border and basolateral membranes of proximal convoluted tubules[16]. Recently it is reported that megalin receptor is present at apical membrane of proximal convoluted tubules which binds and causes endocytosis of Aminoglycosides in proximal tubular cells[18].

The first site of interaction of Aminoglycosides with cells occur at plasma membrane of renal proximal tubular cells which not only causes depression of apical membrane transporter but also causes loss of brush border membrane enzymes and phospholipids which occurs early in the course of Aminoglycosides administration. This includes decreased transport of organic bases, electrolytes (Sodium, Potassium and Calcium) and also causes decreased activity of Na^+-K^+ATPase[9]. Gentamicin causes hypocalcemia and hypomagnesemia at clinical doses demonstrated in a study on normal human beings[8].

In the current study, significant lower levels of potassium (P<0.001) were observed in gentamicin and amikacin treated animals in our study. These results are in agreement with the findings of hypokalemia which was observed by Chou et al in female patients treated with gentamicin[10]. George J. Kaloyanides et al also confirmed the renal depletion due to depression of Na^+-K^+ ATPase[9.] Similarly Patricio et al[11] also described the same results (hypokalemia) associated with renal hypertrophy in both animals and human beings which are again congruent to our findings.

Significantly decreased calcium levels (P<0.001) in gentamicin and amikacin treated animals were observed in our study. The same results were exhibited by Clay Elliott et al who described that Gentamicin administered at normal clinical dose caused renal calcium wasting in normal human beings[12]. The same hypocalcemia was observed by Liamis et al in those patients who were treated with Aminiglycosides at normal doses[17]. But Parsons et al described hypercalcemia mediated by a decrease in calcium re-absorption in early distal tubules[13] which is again congruent to our findings.

CONCLUSIONS

It is well known that Aminoglycosides are highly prescribed drugs since a number of decades, yet they have not only damaging effects on proximal tubular cells in basolateral membrane (BLM) but also lower the serum potassium and calcium levels, thus aggravating their renal damaging effects. So, it is suggested that the electrolyte parameters should be monitored during the course of treatment and if found unusual, should be corrected accordingly. At the same time risk factors and/or concomitant administration of other drugs that cause electrolyte imbalance should be avoided.

REFERENCES

1. Manjunath P. Pai., Anne N. Nafziger, and Joseph S. Bertino, Jr. Antimicrob Agents Chemother: Simplified Estimation of Aminoglycoside Pharmacokinetics in Underweight and Obese Adult Patients, 2011 September; 55(9): 4006–4011.
2. Craig W. A. Optimizing aminoglycoside use. Crit. Care Clin. 27 (2011):107–121.
3. Houghton J. L., Green K. D., Chen W., Garneau-Tsodikova S. The future of aminoglycosides: the end or renaissance? Chembiochem 11 (2010):880–902.
4. Hessen MT, Pitsakis PG, Levison ME Postantibiotic effect of penicillin plus gentamicin versus Enterococcus faecalis in vitro and in vivo. Antimicrobe Agents Chemother 33 (1989): 608-611.
5. Karlowsky JA, Zhanel GG, Davidson RJ, Hoban DJ Postantibiotic effect in Pseudomonas aeruginosa following single and multiple aminoglycoside exposures in vitro. J Antimicrob Chemother 33 (1994): 937-947.
6. Emanuele Durante-Mangonia, Alexandros Grammatikos, Riccardo Utili, and Matthew E. Falagas. Do we still need the aminoglycosides?: International Journal of Antimicrobial Agents, Volume 33, Issue 3, March 2009, Pages 201–205
7. R. Zietse, R. Zoutendijk & E. J. HoornFluid, electrolyte and acid–base disorders associated with antibiotic therapy: Nature Reviews Nephrology 5, 193-202 (April 2009)
8. Elliott C, Newman N, and Madan A. Gentamicin effects on urinary electrolyte excretion in healthy subjects: Clin Pharmacol Ther, 2000 Jan;67(1):16-21
9. George J. Kaloyanides. Aminoglycoside-induced functional and biochemical defects in the renal cortex: Fundamental and Applied Toxicology, Volume 4, Issue 6, December 1984, Pages 930–943
10. Chou, Chu-Lin MD; Chen, Yeong-Hwang MD; Chau, Tom MD; Lin, Shih-Hua MD. Acquired Bartter-Like Syndrome Associated with Gentamicin Administration: American Journal of the Medical Sciences: March 2005 - Volume 329 - Issue 3 - pp 144-149
11. Patricio E Ray, Shin-Ichi Suga, Xue-Hui Liu, Xiuling Huang and Richard J Johnson. Chronic potassium depletion induces renal injury, salt sensitivity, and hypertension in young rats: Kidney International 2001, 59, 1850–1858; doi:10.1046/j.1523-1755.2001.0590051850.x
12. Clay Elliott MD, Nancy Newman MS and Arvind Madan MD. Gentamicin effects on urinary electrolyte excretion in healthy subjects: Clinical Pharmacology & Therapeutics 2000 67, 16–21; doi: 10.1067/mcp.2000.103864
13. Parsons PP, Garland HO and Harpus ES. Localization of the nephron site of gentamicin induced hypercalciuria in rats: a micropuncture study. Br J Pharmacol 2000; 130(2): 441-49
14. David C. Dugdale. Electrolytes. A.D.A.M., Inc. [internet] 2011 Sep. 09 [2013 Oct. 04];Available from: URL : http://www.nlm.nih.gov/medlineplus/ency/article/002350.htm
15. Melissa Conrad Stoppler. Electrolytes. MedicineNet [internet] [2013 Oct. 04]
16. Available from: URL: http://www.medicinenet.com/electrolytes/article.htm
17. The Scott Hamilton CARES initiative. Electrolyte Imbalance [internet] [2013 Oct. 04]. Available from: URL: http://chemocare.com/chemotherapy/side-effects/electrolyte-imbalance.aspx#.Uk71doYQbQs
18. Liamis G, Milionis HJ, Elisaf M (2009) A review of drug-induced hypocalcemia. J Bone Miner Metab 27: 635-642.
19. Nagai J, Takano M , Molecular aspects of renal handling of aminoglycosides and strategies for preventing the nephrotoxicity: Drug Metab. Pharmacokin, 19(3): 159-170 (2004).