Original Article

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Electrolyte disorders during vancomycin treatment in hospitalized patients at hematology-oncology wards of Namazi hospital in Shiraz

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Abstract

Increased serum creatinine level and decreased glomerular filtration rate are the major features of vancomycin nephrotoxicity. Electrolyte disorders of this agent have not been considered in relevant clinical studies so far. The aim of the present study was to determine potassium and magnesium disorders in hematology-oncology patients undergoing vancomycin treatment. A cross-sectional, observational study was performed during 9 months at three hematology-oncology wards of Namazi hospital in Shiraz. Patients >18 years of age with no documented history of acute kidney injury or chronic kidney disease having been planned to receive vancomycin for at least 1 week, were recruited. Urine samples for determining creatinine, potassium, and magnesium levels were collected at days 0, 3, 5, 7, 10, and 14 of treatment. Hypokalemia and hypomagnesemia were defined as serum potassium and magnesium levels below 3 mEq/L and 1.2 mEq/L, respectively. Two-fifth (40.38%) of the study population developed hypokalemia during 2 to 3 days after initiating vancomycin. Hypomagnesemia was detected in 5.77% of vancomycin recipients with the time onset of 7.67±3.21 days. The mean±standard deviation of potassium supplement was significantly higher in patients with than those without hypokalemia (P=0.006). No case of renal potassium and magnesium wasting was identified. Amphotericin b co-administration was significantly associated with hypokalemia during vancomycin treatment (odds ratio=0.164 [95% confidence interval=0.041-0.647], P=0.01). In contrast to hypomagnesemia, hypokalemia occurred commonly during the first days of vancomycin treatment. However, the real casual relationship, mechanism, and clinical outcome of these electrolyte disorders in vancomycin recipients remain unclear.

Keywords: Electrolyte disorders, Hematology-oncology wards, Vancomycin.

1. Introduction

Antibiotics have several adverse effects on the kidney. These are manifested mostly by decreased glomerular filtration rate (GFR). However, they can also be associated with electrolyte disorders. Among antibiotics, most electrolyte disorders have been reported with amphotericin B, aminoglycosides, and penicillins (1).

Vancomycin, a glycopeptide antibiotic with anti-gram positive activity, is involved with a number of adverse effects including nephrotoxicity (2). Increased serum creatinine levels and decreased GFR due to acute tubular necrosis or interstitial nephritis are the major features of vancomycin nephrotoxicity (1, 2). A number of studies on the incidence of vancomycin nephrotoxic-

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ity, have been performed in Iran. It ranges largely from 0% to 100% in our population from Iran (3-6). Several demographic, clinical, and paraclinical variables have been suggested as risk factors of vancomycin nephrotoxicity including old age, impaired baseline renal function, longer duration of therapy, intermittent infusion (versus continuous infusion), high trough levels, co-administration of nephrotoxic agents (e.g., aminoglycosides, amphotericin b, furosemide), and concurrent administration of piperacillin-tazobactam or vasoactive drugs (2, 7).

In contrast to the epidemiology of vancomycin nephrotoxicity, electrolyte disorders as a possible adverse effect of this agent, have not been considered in relevant clinical studies so far. The aim of the present preliminary study was to determine potassium and magnesium disorders in hematology-oncology patients recieving vancomycin treatment.

2. Material and methods

A cross-sectional, observational study was performed from August 2015 to April 2016 at two hematology-oncology and one hematopoietic stem cell transplantation wards of Namazi hospital, affiliated to Shiraz University of Medical Sciences, Shiraz, Iran. The medical ethics committee of the hospital approved the study and all patients filled out a written informed consent form.

The criteria considered for recruiting patients into the study were as follows:

1) documented history of AKI defined as an increase in serum creatinine ≥0.3 mg/dl within 48 h, or an increase in serum creatinine by ≥1.5 times baseline within the prior 7 days, or urine volume <0.5 ml/kg/h for 6 h (8);

2) documented chronic kidney disease defined as a creatinine clearance below 60 ml/min/1.73 m^2 or documented history of regular peritoneal or hemodialysis for more than 3 months (9);

3) without documented history of receiving vancomycin within the recent 14 days, and

4) planned to receive vancomycin for at least 1 week.

Demographic (age, sex, weight) and clinical data (vancomycin dose, duration of treatment, and indication, duration of infusion, type of co-administered medications that may exacerbate or attenuate electrolyte disorders) of patients were recorded. Amounts of daily oral and/or intravenous intake of potassium and magnesium as a supplement (rather than dietary intake) during the course of vancomycin treatment, were calculated.

According to routine practice of the wards, serum potassium and magnesium were checked on daily and weekly basis, respectively. Considering the fact that nephrotoxicity typically occurs from 4 to 8 days after the initiation of vancomycin treatment (10), urine samples for determining creatinine, potassium, and magnesium levels, were collected at days 0, 3, 5, 7, 10, and 14 of treatment. Measurement of serum as well as urine creatinine and all of the above electrolytes was performed by an Auto-analyzer (Shanghai Xunda Medical Instrument, China). Hypokalemia was defined as serum potassium level below 3 mEq/L and hypomagnesemia as serum magnesium level less than 1.2 mEq/L (11). The urine potassium to-creatinine ratio above 13 mEq/g in the presence of hypokalemia was considered as renal potassium wasting (12). Renal magnesium wasting was determined as a 4% or more in the fractional excretion of magnesium in patients with hypomagnesemia (13).

2.1. Statistical analysis

Continuous and categorical data were expressed as mean±standard deviation (SD) or standard error (SE) and percentages, respectively. Univariate and multivariate logistic regression analyses with odds ratio (OR) and 95 % confidence interval (CI) were used to determine associated factors of electrolyte disorders. In univariate analysis, the possible association of each independent variable including age, gender, baseline serum electrolyte values, cumulative dose of vancomycin, vancomycin indication, co-administration of aminoglycosides, calcineurin inhibitors, amphotericin b, acyclovir, loop diuretics (furosemide), and potassium sparing diuretics (spironolactone) with electrolyte disorders (as dependent variable), was assessed separately. Those with P values less than 0.05 were thereafter considered together for multivariate logistic regression analysis. All statistical analyses were performed by the Statistical Package for the Social Sciences (SPSS) version 20

software (IBM company, New York, NY, United States).

3. Results and Discussion

Among 71 patients having been planned to receive vancomycin during the study period, 52 individuals met the inclusion criteria and were recruited into the study. Thirty four patients were male and 18 were female.. Their mean±SD of age was 43.38±16.46 years.

Twenty one (40.38%) patients developed hypokalemia during the course of vancomycin treatment. The mean±SE of onset of hypokalemia was 2.73 0.64 days. The rate of hypomagnesemia was 5.77%. Hypomagnesemia developed 7.67±3.21 days after initiating vancomycin. The mean±SE of urine potassium to-creatinine ratio at days 0, 3, 5, 7, 10, and 14 of treatment, was 0.82±0.09, 0.73±0.07, 0.81±0.09, 0.83±0.08, 0.81±0.13, and 0.47±0.11 mEq/g, respectively. No case of renal potassium and magnesium wasting was identified. The mean±SE of potassium and magnesium supplement given was 44.68±6.28 and 0.53±0.39 meq/day, respectively. The mean±SD of potassium supplement was significantly higher (P=0.006) in patients with (65.04±42.03 meq/day) than those without (30.88±42.64 meq/day) hypokalemia.

According to univariate logistic analysis, sex (P=0.007), amphotericin b co-administration (P=0.005), and duration of vancomycin treatment (P=0.044), were selected among studied variables for multivariate regression analysis. Based on this final model, amphotericin b co-administration significantly associated with hypokalemia during vancomycin treatment (OR=0.164 [95% CI=0.041-0.647], P=0.01) (Table 1). The mean±SD of time interval between vancomycin and amphotericin b initiation was 2±0.85 days. Its minimum-maximum value was 0-3 days. Considering the low frequency of hypomagnesemia, performing logistic regression analysis for determining associated factors of this electrolyte disorder was not statistically feasible. No patient was given cisplatin, ifosfamide, cyclophosphamide, aminoglycosides, cephalosporins, and penicillins during the study period.

More than two-fifths of our population developed hypokalemia during 2 to 3 days after initiating vancomycin therapy. According to current literature, there is only one published case report in this regard. Keith Siau presented and described a 68-year-old female with an infected hindquarter amputation site that developed hypokalemia (a drop of serum potassium from 4.2 mEq/L to 2.9 mEq/L) one week after starting vancomycin. The patient re-experienced two more clinically significant episodes of hypokalemia that caused pulseless ventricular tachycardia during the course of vancomycin and oral furosemide co-treatment. Termination of vancomycin course along with administering potassium supplements and a potassium sparing diuretic (amilorode) led to complete resolution of hypokalemia in the patient. Renal wasting was postulated by the author as the mechanism of vancomycin induced hypokalemia (14). In contrast to this hypothesis, our results demonstrated no case of renal potassium and magnesium wasting during the course of vancomycin treatment. Therefore, vancomycin may induce hypokalemia through other unknown mechanisms.

Among antibiotics, electrolyte imbalances such as hypokalemia and hypomagnesemia are well recognized with aminoglycosides and amphotericin b (1). Aminoglycosides exert their nephrotoxic effects mainly in the proximal tubule via different pathways including the inhibition of microsomal protein synthesis, mitochondrial dysfunction, impaired generation of ATP that decrease the activity of basolateral Na^+/K^+ ATPase, inhibition of phosphatidylinositol cascade, and lysosomal instability. Increase in fractional renal excretion of Mg^{2+} and Ca^{2+} secondary to alteration in the transport of these ions in the distal tubule, has been also demonstrated in experimental and clinical studies (1). It is noteworthy that no patient in our study had received aminoglycosides concurrently with vancomycin. In contrast to aminoglycosides, predominant effect site of amphotericin b on electrolytes especially potassium, are in the distal tubule. By creating pores in cell membranes, amphotericin b increases membrane permeability to potassium that leads to potassium wasting and consequently, hypokalemia can occur (1). Amphotericin b-induced hypokalemia and hypomagnesemia are common adverse events with the reported

frequency of 75-90% (15) and 15-100% (16) in the literature, respectively.

Among studied demographic, clinical, and paraclinical variables, only amphotericin b co-administration considered as an independent associated factor of hypokalemia in our population during vancomycin treatment. This finding is largely predictable considering the high prevalence of amphotericin b-induced electrolyte disorders and the synergistic nephrotoxic effects of

Table 1. Comparison of different demographic, clinical, and paraclinical features in patients with and without hypokalemia during vancomycin treatment.

Variable	With hypokalemia (n=21)	Without hypokalemia (n=31)	Univariate model		Multivariate model	
			P value	OR (95% CI)	*P* value	OR (95% CI)
Age (years)						
Mean±SD	44.81±13.02	42.39±18.58	0.6	1.009 (0.975-1.044)	---	---
Range	23-66	20-81				
Gender (%)						
Male	9 (42.86)	25 (80.65)	0.007	5.556 (1.606-9.223)	0.069	5.357 (1.283-9.366)
Female	12 (57.14)	6 (19.35)				
Baseline serum potassium (meq/lit)						
Mean±SD	4.16±0.85	4.31±0.93	0.41	1.336 (0.996-5.331)	---	---
Range	3.31-5.42	3.92-5.87				
Vancomycin indication (%)						
Treatment of febrile neutropenia	17 (80.95)	28 (90.32)	0.339	2.196 (0.437-11.027)	---	---
Others	4 (19.05)	3 (9.68)				
Vancomycin treatment duration (days)						
Mean±SD	17.57±6.79	13.55±6.34	0.044	1.099 (1.003-1.025)	0.182	1.075 (0.966-1.197)
Range	9-36	7-33				
Vancomycin cumulative dose (g)						
Mean±SD	27.81±19.99	25.74±13.76	0.653	1.008 (0.974-1.043)	---	---
Range	18-72	14-66				
Co-administration of acyclovir (%)						
Yes	19 (90.48)	24 (77.42)	0.235	0.361 (0.067-1.942)	---	---
No	2 (9.52)	7 (22.58)				
Co-administration of amphotericin b (%)						
Yes	14 (66.67)	8 (38.09)	0.005	0.174 (0.052-0.585)	0.01	0.164 (0.041-0.647)
No	7 (33.33)	23 (74.19)				
Co-administration of furosemide (%)						
Yes	4 (19.05)	4 (12.9)	0.549	0.63 (0.139-2.859)	---	---
No	17 (80.95)	27 (87.09)				
Co-administration of cyclosporine (%)						
Yes	3 (14.29)	2 (6.45)	0.358	0.414 (0.063-2.721)	---	---
No	18 (85.71)	29 (93.55)				
Co-administration of spironolactone (%)						
Yes	3 (14.29)	7 (22.58)	0.168	0.677 (0.035-4.252)	---	---
No	18 (85.71)	24 (77.42)				

amphotericin b and vancomycin. However, most patients in our study received amphotericin b as a part of febrile neutropenia treatment regimen. According to prominent guidelines of antimicrobial agents in neutropenic patients, empirical therapy with antifungal agents such as amphotericin b is usually initiated 2 days after starting vancomycin (17). Therefore, hypokalemia mostly developed at the first day of amphotericin b treatment and this temporal hierarchy precludes the idea that amphotericin b is an initiating or causative factor of hypokalemia in our vancomycin recipients. Vancomycin-induced hypokalemia seems to be both dose- and duration-independent. In line with this issue, vancomycin serum concentration is within the therapeutic range in the aforementioned case report (14).

Severe hypokalemia and hypomagnesemia induced by medications can cause metabolic complications, rhabdomyolysis, and life-threatening arrhythmias (1). Two episodes of pulseless ventricular tachycardia occurred in the above case report of vancomycin-induced hypokalemia (14). Fortunately, these adverse events were not observed in our population at least during the course of vancomycin treatment. Based on the onset and severity of hypokalemia/hypomagnesemia, oral or intravenous potassium/magnesium supplementation may be required (16, 18). Administering potassium sparing diuretics including amiloride (5 mg orally twice daily) and spironolactone (100 mg orally twice daily) has been shown to be effective in the prevention or management of hypokalemia caused by amphotericin b (19). In case of co-existing hypomagnesemia, its correction will facilitate the resolution of hypokalaemia (18).

The study suffers from three major limitations. First, the sample size of the study was relatively small. This is mainly due to implementing several exclusion criteria and the preference of teicoplanin over vancomycin by some attending hematologist-oncologists for the management of febrile neutropenia. Second, the limited number of urine sampling (6 times) and serum magnesium level measurement (once a week) due to practical problems, may underestimate the frequency of hypomagnesemia and electrolyte renal wasting observed in our survey. Third, trough level of vancomycin as a possible risk factor of electrolyte disorders was not measured and taken into account due to lack of financial resources.

4. Conclusion

Two-fifths of our population developed hypokalemia during 2 to 3 days after initiating vancomycin. Hypomagnesemia was detected in 5.77% of vancomycin recipients with the time onset of 7.67±3.21 days. No case of renal potassium and magnesium wasting were identified. Amphotericin b co-administration was considered as an independent associated factor of hypokalemia within the time of vancomycin treatment. No serious complication relevant to hypokalemia/hypomagnesemia was identified during the course of vancomycin treatment. All episodes of electrolyte disorders were managed by either potassium/magnesium supplementation or co-administration of spironolactone. The real casual relationship of electrolyte imbalances with vancomycin treatment and its relevant, possible mechanisms are questions that remain to be answered in the future experimental and clinical studies.

Conflict of interest

None declared.

5. References

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