Prevalence of Hyperkalemia in Adult Patients Taking Spironolactone and Angiotensin Converting Enzyme Inhibitors or Angiotensin Receptor Blockers

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Background: *Hyperkalemia is common when spironolactone and angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) are combined.*
Objective: *To determine the prevalence and risk factors of hyperkalemia in adult patients taking spironolactone and ACEIs or ARBs.*
Material and Method: *A retrospective descriptive study was conducted. Adult patients taking spironolactone and ACEIs or ARBs who visited the outpatient department of Siriraj Hospital between January and December 2009 were included. Exclusion criteria were chronic kidney disease patients who had undergone dialysis and patients with hyperkalemia from other causes. The authors defined hyperkalemia as serum potassium of more than 5.0 mmol/L.*
Results: *Five hundred thirty four patients were included during the study period. The prevalence of hyperkalemia was 11.2% (60 patients). The risk factors of hyperkalemia were chronic kidney disease (OR 2.47, 95% CI 1.07-5.70), initial serum potassium level >4.0 mmol/L (OR 2.65, 95% CI 1.44-4.88), and dosing of spironolactone more than 25 mg per day (OR 2.42, 95% CI 1.23-4.74).*
Conclusion: *The prevalence of hyperkalemia in adult patients taking spironolactone and ACEIs or ARBs is 11.2%. Risk of hyperkalemia is chronic kidney disease, high serum potassium, and high spironolactone use.*

Keywords: *Spironolactone, Angiotensin-converting enzyme inhibitors, Angiotensin receptor blockers, Hyperkalemia, Drug interaction*

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Drug interaction is the unwanted reaction resulting from one drug's effect is altered by another drug. This interaction change pharmacological activity, clinical efficacy, therapeutic outcome and in some situation may increase its toxicity. Drug interaction can be prevented by understanding pharmacological property of individual drug and the risk factors relating to its interaction.

In 2004, Prybys[1] studied the drug interaction rate in the United States. Hyperkalemia, due to drug interaction is a common problem found in the emergency room, especially in patients taking a combination of Angiotensin-converting enzyme inhibitors (ACEIs) or Angiotensin receptor blockers (ARBs) and spironolactone[2-4].

Currently, a combination of ACEIs or ARBs with spironolactone has been widely used after a Randomized Aldactone Evaluation Study (RALES) was published in 1999[5]. Spironolactone usage among heart failure patients who already received ACEIs or ARBs was increased from 0.34-3.0% to 14.9-21.3%[6,7].

Even though RALES reported only 2% hyperkalemia, a retrospective cohort study by Sadjadi et al[8] found 24% hyperkalemia in patients taking combination of spironolactone with ACEIs or ARBs. In 2004, Pitt B et al compared admission rate due to hyperkalemia before and after RALES publication. They found an increase of 4.5 times (from 0.24% to 1.1%). Furthermore, in patient mortality rate from hyperkalemia was also increased by seven times (from 0.03% to 0.2%)[6].

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However, there has never been a study about the prevalence and risk factors of hyperkalemia among this population in Thailand.

Outcome measurement

The primary outcome was to determine the prevalence of hyperkalemia in patients taking spironolactone and ACEIs or ARBs. Secondary outcome was to define the risk factors.

Material and Method

The method was a retrospective descriptive study conducted by reviewing out-patient card of Siriraj Hospital patients between January 1 and December 31, 2009. Inclusion criteria was patients more than 18 years old who were receiving a combination of spironolactone and ACEIs or ARBs but excluded chronic kidney disease patients receiving dialysis or patients diagnosed with hyperkalemia from other causes.

Previous studies used different definitions for hyperkalemia but the present study defined hyperkalemia as serum potassium is more than 5.0 mmol/L according to definition of a review in critical care patients[9].

Statistical analysis

Sample size was at least 288 patients after calculated by using estimating proportion of one group formula and 20% added. Numerical data were calculated by using mean and standard deviation or median, minimum and maximum. Risk factors were assessed using Chi-square or Fisher's exact test for categorical data and Independent t-test or Mann-Whitney U test for numerical data. Multivariable logistic regression was used to model the significant factors.

The presented study was approved by Siriraj Institutional Review Board and had a project code of 571/2553 (EC4) with document number Si562/2010.

Results

After reviewing 790 outpatient charts at Siriraj Hospital between January and December 2009, 678 patients met the inclusion criteria but 13 patients were excluded due to chronic kidney disease undergoing dialysis and also 131 who had no documentation of serum potassium level during the study period. Therefore, only 534 patients were analyzed.

Patients taking combination of spironolactone and ACEIs or ARBs had mean age of 61.5 years old (19-96 years old) and 57.4% were men. Most patients had more than one co-morbidities most common underlying diseases were 205 (38.6%) with diabetes mellitus, 327 (61.6%) with hypertension, 181 (34.2%) with coronary artery disease and 48 (9.1%) with liver cirrhosis respectively. Mean initial serum potassium and creatinine was 4.0 mmol/L and 1.1 mg/dL as shown in Table 1. There were 60 patients who had serum potassium more than 5.0 mmol/L after using sipronolactone with ACEI or ARB which lead to 11.2% prevalence.

Sixty patients had hyperkalemia. However, only medication treatment with kalimate was used. No patient needed treatment with dialysis and there was no morbidity or mortality from hyperkalemia

Table 1. Demographic data of enrolled patients

Characteristic, mean (SD)	Total (n = 534)	Hyperkalemia (n = 60)	Non-hyperkalemia (n = 374)	p-value
Age (y)	61.5 (14.3)	60.8 (15.1)	61.6 (14.2)	0.82
Male	292 (57.4)	37 (61.7)	255 (58.8)	0.24
Underlying disease				
DM	205 (38.6)	38 (63.3)	176 (37.1)	0.06
HT	327 (61.6)	25 (41.7)	289 (61.0)	0.51
Heart failure	303 (57.1)	14 (13.3)	265 (55.9)	0.16
ACS	181 (34.2)	25 (41.7)	156 (32.9)	0.12
Cirrhosis	48 (9.1)	14 (23.3)	34 (7.2)	<0.001
CKD	44 (8.3)	9 (15.0)	35 (7.4)	0.04
Others	429 (80.3)	38 (63.3)	391 (82.5)	0.15
Serum creatinine (mg/dl)	1.1 (0.37)	1.2 (0.5)	1.1 (0.4)	0.13
Serum potassium (mmol/L)	4.0 (0.5)	4.2 (0.5)	4.0 (0.5)	0.01

DM = diabetes mellitus; HT = hypertension; ACS = acute coronary syndrome; CKD = chronic kidney disease

reported. However, data about electrical change or clinical effect from hyperkalemia was not collected in the present study.

To define risks of hyperkalemia, the authors found five dehydrated patients in only the hyperkalemic group that made this factor statistically significant. The other affecting factors were liver cirrhosis, chronic kidney disease, and initial serum potassium level of >4.0 mmol/L. Among potassium affecting medication, only NSAIDs and high spironolactone daily dose (>25 mg/day) were the significant factors as shown in Table 2.

After using multivariable logistic regression model, there were only three statistical significant factors induced hyperkalemia that were chronic kidney disease, initial serum potassium level >4.0 mmol/L, and spironolactone use >25 mg/day, as shown in Table 3.

When compared between patients taking ACEIs and ARBs group, the prevalence of hyperkalemia were found to be 13.4% and 7.7% respectively with p-value 0.04. Factors found to be statistically significant difference between these groups are age, male, hypertension, high initial serum creatinine level, and spironolactone use >25 mg/day as shown in Table 4.

Discussion

From the results, the prevalence of serum potassium more than 5.0 mmol/L in adult patients taking combination of spironolactone and ACEIs or ARBs is 11.2%, which is more than previously reported by RALES study[5]. However, when compared to Bozkurt's study, prevalence of hyperkalemia in the authors' study is lower. This may be due to a higher ratio of renal insufficiency and potassium supplement (30.7% and 40.4% respectively) in Bozkurt's study[10]. The prevalence of hyperkalemia in Cruz's study was also higher. This can be explained by their higher initial serum potassium rate (initial potassium >5 mmol/L) and 76.5% of their population had rising creatinine level at the end of the study[11].

Table 2. Concurrent potassium-affecting medication use

Medication, mean (SD)	Total (n = 534)	Hyperkalemia (n = 60)	Non-hyperkalemia (n = 474)	p-value
Spironolactone >25 mg/day	104 (19.5)	22 (38.3)	82 (17.3)	<0.001
ACEIs	325 (60.9)	40 (66.7)	285 (60.1)	0.09
ARBs	209 (36.8)	16 (26.7)	193 (40.7)	0.08
NSAIDs	2 (0.4)	2 (3.3)	0 (0.0)	0.01
Diuretics	376 (70.4)	42 (70.0)	334 (70.4)	0.63
Thiazide	24 (4.5)	4 (6.7)	20 (4.2)	
Loop diuretics	352 (65.9)	38 (63.3)	314 (66.2)	
Digitalis	160 (30.0)	21 (35.0)	139 (29.3)	0.37
Potassium supplement	7 (1.3)	2 (3.3)	5 (1.1)	0.18

ACEIs = angiotensin-converting enzyme inhibitors; ARBs = angiotensin receptor blockers; NSAIDs = non-steroidal anti-inflammatory drugs

Table 3. Multivariable logistic regression of factors affecting hyperkalemia

Risk factor	Hyperkalemia (%)*	Crude OR (95% CI)	Adjusted OR (95% CI)	p-value
Cirrhosis	29.2	4.09 (2.04-4.20)	2.04 (0.91-4.56)	0.080
Chronic kidney disease	20.5	2.37 (1.07-5.22)	2.47 (1.07-5.70)	0.030
Serum K >4.0	15.3	2.69 (1.50-4.81)	2.65 (1.44-4.88)	0.002
Spironolactone >25 mg/day	21.2	2.76 (1.55-4.91)	2.42 (1.23-4.74)	0.010
NSAIDs**	100.0	-	-	0.999
Dehydration**	100.0	-	-	0.999

* Percentage = $\frac{\text{Number of hyperkalemic patient with risk factor}}{\text{Number of all patients with risk factor}} \times 100$

** Cannot calculate OR because there were cases only in hyperkalemic group

Table 4. Compare data between ACEIs and ARBs group

Characteristics, mean (SD)	Total (n = 534)	ACEIs (n = 325)	ARBs (n = 209)	p-value
Age (y)	61.5 (14.3)	58.7 (14.0)	65.7 (13.8)	0.002
Male	292 (57.4)	202 (62.2)	91 (43.5)	<0.001
Underlying disease				
DM	205 (38.6)	124 (38.2)	83 (39.7)	0.06
HT	327 (61.6)	182 (56.0)	149 (71.3)	<0.001
Heart failure	303 (57.1)	196 (60.3)	109 (52.2)	0.13
ACS	181 (34.2)	102 (31.4)	79 (37.8)	0.08
Cirrhosis	48 (9.1)	32 (9.8)	16 (7.7)	0.44
CKD	44 (8.3)	23 (7.1)	21 (10.0)	0.19
Others	429 (80.3)	263 (80.9)	171 (81.8)	0.64
Serum creatinine (mg/dl)	1.1 (0.37)	1.0 (0.3)	1.1 (0.4)	0.04
Serum potassium (mmol/L)	4.0 (0.5)	3.9 (0.5)	4.0 (0.5)	0.49

Mean serum potassium level in the authors' study is 5.5 mmol/L (SD 0.41). All patients were treated promptly without complication because most of the patients were monitored closely. Therefore, there is no death reported but clinical significant effect cannot be obtained due to inadequacy of data.

Even though, many published studies reported prevalence of hyperkalemia in patients taking combination of spironolactone and ACEIs or ARBs as mentioned earlier but only a few studies with a small sample size indicated the risk factors related to hyperkalemia such as, Schepkens et al with a case series of 25 patients taking a combination of spironolactone and ACEIs reported that age, renal insufficiency, diabetes mellitus, worsening heart failure, and dehydration were the significant risk factors[4]. Wrenger's study, a case series of 44 patients taking combination of spironolactone and ACEIs or ARBs, found that the risk factors were advanced age, spironolactone dose >25 mg/day, renal insufficiency, and diabetes mellitus[12]. However, these two studies had a small sample size so a clear cut conclusion on risk factors cannot be drawn but when compared with the present study, several common risk factors were renal insufficiency and spironolactone dose >25 mg/day.

Subgroup analysis was performed and found that there was higher hyperkalemia in ACEIs group. This might be because ACEIs population received higher spironolactone daily dose (24% in ACEIs and 12.9% in ARBs groups).

Limitation

There is no data about indication for using spironolactone with ARB/ACEI in each patient. These can reflect the medication need and useful for physicians to decide whether they should initiate these drugs or not.

When compared to previous studies, the authors' study has a larger sample size and the population has multiple co-morbidities, which reflects the real patient seen in daily clinical practice. However, because this is a descriptive retrospective study, inadequacy in obtaining data and a bias in data documentation is unavoidable. Moreover, because the patients were not followed from the beginning use of medications, there might be confounding factors in defining the risk factors. In future, a multicenter prospective cohort study with a larger sample size is needed to increase reliability of the result and minimize the limitation mentioned earlier.

Conclusion

Adult patients receiving combination of spironolactone and ACEIs or ARBs had a prevalence of hyperkalemia of 11.2%. The affecting risk factors were chronic kidney disease, initial serum potassium level >4.0 mmol/L, and spironolactone use >25 mg/day. Results of the presented study may convince prescribing physicians to recognize the possible drug interaction between these medications. Closed monitoring of potassium level in high-risk patients can prevent unwanted morbidity and mortality.

Potential conflicts of interest

None.

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ความชุกของการเกิดโพแทสเซียมในเลือดสูงในผู้ป่วยผู้ใหญ่ที่ได้รับยาสไปโรโนแลคโตนร่วมกับยายับยั้งเอนไซม์เปลี่ยนแองจิโอเทนซินหรือยาปิดกั้นตัวรับแองจิโอเทนซิน

อุษาพรรณ สุรเบญจวงศ์, ณัฐ ตันพิพัฒน์, สมฤดี ฉัตรสิริเจริญกุล, อภิชญา มั่นสมบูรณ์

ภูมิหลัง: *ภาวะโพแทสเซียมในเลือดสูงเป็นภาวะที่เกิดจากอันตรกิริยาระหว่างยาที่พบได้บ่อยเมื่อมีการใช้ยาในกลุ่ม angiotensin-converting enzyme inhibitors (ACEIs) หรือ angiotensin receptor blockers (ARBs) ร่วมกับ spironolactone อย่างไรก็ตามในประเทศไทยยังไม่เคยมีการศึกษาความชุกและปัจจัยเสี่ยงของการเกิดภาวะนี้*

วัตถุประสงค์: *เพื่อหาความชุกและปัจจัยเสี่ยงของการเกิดภาวะโพแทสเซียมในเลือดสูงของผู้ป่วยผู้ใหญ่ที่ได้รับยา spironolactone ร่วมกับยาในกลุ่ม ACEIs หรือ ARBs*

วัสดุและวิธีการ: *เป็นการศึกษาย้อนหลังเชิงพรรณนา โดยทบทวนเวชระเบียนผู้ป่วยผู้ใหญ่ที่มารับบริการที่แผนกผู้ป่วยนอกโรงพยาบาลศิริราช ในช่วงเดือนมกราคม ถึง เดือนธันวาคม พ.ศ. 2552 มีเกณฑ์การคัดเลือกประชากรออกคือ ผู้ป่วยโรคไตวายเรื้อรังที่ได้รับการล้างไต และผู้ป่วยที่เกิดภาวะโพแทสเซียมในเลือดสูงจากสาเหตุอื่น โดยกำหนดให้ระดับโพแทสเซียมมากกว่า 5.0 mmol/L หมายถึงภาวะโพแทสเซียมในเลือดสูง*

ผลการศึกษา: *มีผู้ป่วยที่ได้รับยา spironolactone ร่วมกับยาในกลุ่ม ACEIs หรือ ARBs จำนวน 534 ราย และพบโพแทสเซียมในเลือดสูงคิดเป็นความชุกเท่ากับ 11.2% (60 ราย) ปัจจัยเสี่ยงได้แก่ โรคไตวายเรื้อรัง (OR 2.47, 95% CI 1.07-5.70) โพแทสเซียมในเลือด ณ ช่วงเริ่มต้นมากกว่า 4.0 mmol/L (OR 2.65, 95% CI 1.44-4.88) และ spironolactone มากกว่า 25 mg ต่อวัน (OR 2.42, 95% CI 1.23-4.74)*

สรุป: *ความชุกของการเกิดภาวะโพแทสเซียมในเลือดสูงในผู้ป่วยผู้ใหญ่ที่ได้รับยา spironolactone ร่วมกับยาในกลุ่ม ACEIs หรือ ARBs เท่ากับ 11.2% โดยโรคไตวายเรื้อรัง มีระดับโพแทสเซียมในเลือดสูงหรือได้รับ spironolactone ปริมาณมาก จัดเป็นปัจจัยเสี่ยงซึ่งควรมีการติดตามเฝ้าระวังการเกิดภาวะโพแทสเซียมในเลือดสูงในผู้ป่วยกลุ่มนี้อย่างใกล้ชิด*