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Acute Kidney Injury Hyperkalemia in Patients Undergoing Renin-Angiotensin-Aldosterone Blockade

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Abstract

Introduction: In order to minimize the risk of hyperkalemia (hK^+) in patients with heart failure (HF), in 2005 and 2009 ACC/AHA (American College of Cardiology; American Heart Association) joint guidelines recommended associating renin-angiotensin system (RAS) inhibition with low-dose ALD-block in patients with serum creatinine (sCr) less than 2.5 mg/dl and serum potassium (sK^+) lower than 5 mEq/l. A prevalence of HF in individuals aged 65 and over with mild renal failure at risk of hyperkalemia is steeply increasing. Such data has persuaded us to analyze the association between over-65 HF standard treatment and hK^+.

Aim: This observational retrospective study analyzed emergency room admissions aged 65 and over undergoing ACEI with ALD-block or potassium sparing diuretics (K^+-sparing) and hK^+ ($sK^+ > 6$ mEq/l) over a one year period, from January to December 2010.

Methods: 8,407 over-65 emergency admissions of 62,348 adult entries have been selected from the hospital database. Data was matched with the Local Medical District pharmaceutical database with joint use of ACEI and ALD-block or K^+-sparing medications. Acute Kidney Injury (AKI) was defined according to AKIN (Acute Kidney Injury Criteria) guidelines.

Results: ACEI with spironolactone or K^+-sparing was found in 332 (3.9%) out of the 8,407 over-65 emergency admissions. Seven HF patients (2.1% aged 79-82, 5F 2M) of 332 had hK^+ (sK^+, 6.3-8.5 mEq/l). Six patients had spironolactone and 1 K^+-sparing treatment. sCr before admission was available in 3 (sCr, 1.1-1.4 mg/dl) out of 7 patients, all of which developed AKI. All 7 patients with hK^+ received conservative medical treatment only.

Conclusions: hK^+ occurred in 7 (2.1%) out of the 332 HF over-65 emergency admissions on ACEI. It might suggest a strict application of the current ACC/AHA guidelines with a closer follow-up for those HF patients at risk of developing AKI and hK^+.

Keywords: Angiotensin-converting enzyme inhibition; Aldosterone blockade; Emergency; Heart failure; Hyperkalemia; Potassium-sparing diuretics

Introduction

Renin-angiotensin system (RAS) is the main regulator of extracellular fluid (ECF) volume adjusting glomerular blood flow and tubular sodium reabsorption [1]. Renin is primarily stored in the juxtaglomerular apparatus, but under pathological conditions it can manifest in other regions of the kidney such as podocytes. Angiotensin-converting enzyme (ACE) is released by proximal and distal tubules, mesangial cells and podocytes [2]. ACE converts angiotensin (ANG) I in ANG II and via the activation of ANG type 1 receptor (AT_1R) mediates afferent and efferent arteriolar glomerular vasoconstriction. AT_1R stimulation induces aldosterone release from the adrenal cortex enhancing sodium and water reabsorption. Recent studies provide evidence that cardiac myocytes, fibroblast and vascular smooth cells have an intracellular RAS. ß-adrenergic stimulation of cardiac myocytes causes intracellular and extracellular synthesis of ANG II. Acute injury as glucose exposure of myocytes induces intracellular ANG II production [3]. Myocardial infarction activates cardiac RAS [4] inducing hypertrophy and fibrosis [5]. ANG II stimulates the adrenal cortex to synthesize aldosterone. Although its signals and purpose haven't been completely understood, we know that inducing aldosterone on distal nephron sodium and water absorption controls ECF expansion, eventually regulating systemic blood pressure [6].

Since the late 1990's clinical data has shown that aldosterone blockade (ALD-block) significantly reduces heart failure (HF) mortality. RALES and EPHESUS studies demonstrated that HF patients with NYHA class III and IV have beneficial effects when mineral corticoid receptor blockade is added to ACE inhibition (ACEI) [7,8]. However, an observational study by Albert et al. [9] on 43,625 HF hospitalized patients from 241 hospitals reported that only one-third of HF eligible patients received ALD-block as suggested by current guidelines [10,11]. The authors concluded that several factors may slow the assimilation of aldosterone antagonists in patients with HF and among them: a) case reports of hK^+ during ALD-block [12]; b) prescription of potassium sparing diuretics (K^+-sparing) rather than ALD-block.

Epidemiology analysis estimates that a prevalence of elderly patients with HF and chronic renal disease (CKD) is progressively increasing [13,14]. Elderly individuals with CKD and HF appear also at higher risk of developing hyperkalemia (hK^+) when ACEI [13] or ANG II receptor blockers (ARB) are added to ALD-block. Aim of the present retrospective study was to verify the safety of ALD-block in elderly individuals with HF under standard treatment [10,11] at risk of developing hK^+. The present work has analyzed emergency admission of elderly individuals using hospital and local Medical District databases.

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Methods

Adult emergency entries have been analyzed over a one-year period. Study criteria inclusion was: a) age 65 and over, b) citizen registered with the Italian National Health Service within the Pavia Medical District (Region of Lombardy, Northwest Italy). At admission their data was matched with Local Medical District and Department of Pharmacology databases. It allowed us to identify their family doctor's drug prescriptions. Patients, or their next of kin, were interviewed in order to ascertain compliance to treatment. ACEI and ALD-block association was analyzed according to current ACC/AHA (American College of Cardiology; American Heart Association) HF treatment guidelines [10,11].

Admission with hK^+ was characterized by serum potassium (sK^+) > 6 mEq/l at entry. Acute Kidney Injury (AKI) was defined according to AKIN (Acute Kidney Injury Criteria) guidelines [15].

In order to avoid patient identification, statistical analysis was carried out using codes given at hospital entry. Statistical analysis was performed using open source OpenOffice.org Calc [16]. Study approval was granted by the local hospital Ethical Committee.

Results

A total 62,348 adult emergency entries were evaluated during the year 2010. Of entries 5,864 patients over 65 had single or multiple emergency admissions, but only 5,755 individuals with 8,407 entries matched the aforementioned criteria. 70% of drug history (DH) taken at the time of admission matched drug prescriptions retrieved by the Local Medical District database. In cases where the data didn't match, the DH taken at the time of admission wasn't eligible for statistical analysis.

332 out of 5,755 patients over 65 (5.8%) were undergoing HF treatment with ACEI and ALD-block or K^+-sparing treatment. Before hospital admission 123 (37%) of the 332 HF individuals were under K^+-sparing instead of ALD-block (Table 1). hK^+ and/or AKI with metabolic acidosis were observed on admission in 7 (2.1%) and 3 (0.9%) of the 332 HF patients respectively (Table 2). 3 patients under ACEI with hK^+ developed documented AKI (Tables 3 and 4). 6 out of 7 HF patients over 65 were treated with ALD-block and 1 patient was under K^+-sparing therapy (Table 3). One patient with high sK^+ levels (5.9 mEq/l) was taking ACEI and ALD-block at the time of admission (Table 4 and 5). The odds ratio (OR) of HF patients under ACEI and ALD-block or K^+ sparing therapy was 0.03.

The day after admission, improvement in renal function and sK^+ lowering were obtained in 6 out of 7 patients with hK^+. In one case a blood test couldn't be carried out the day after admission (Table 4). Nevertheless, an improvement in renal function and sK^+ in normal range were documented within 12 months from hospital discharge (Table 4).

Hemodialysis was never performed. One patient with hK^+ died during hospitalization, but the cause of death couldn't be retrieved from our databases (Tables 3 and 4).

	Creatinine criteria	Urine Output criteria
Stage 1	↑ Cr x 1.5 or Cr > 0.3 mg/dl	UO < 0.5 ml/kg/hr x 6-hr
Stage 2	↑ Cr x 2	UO < 0.5 ml/kg/hr x 12-hr
Stage 3	↑ Cr x 3 or Cr ≥ 4 mg/dl	UO < 0.3 ml/kg/hr x 24-hr or anuria × 12-hr

↑: increase *vs* basal; Cr: creatinine mg/dl; UO: Urine Output; hr: hour

Table 1: AKIN (Acute Kidney Injury Criteria) classification [15].

Discussion

The population of those 65 and over as well as the heart and renal failure epidemic, are progressively growing. The need for ACEI and ALD-block was a priority already in the late 1990's [7]. According to

Age years, M ± SD (range)	77.3 ± 7.7 (65-103)
Sex No (%)	M = 2,440 (42.4) F = 3,315 (57.6)
ACEI + ALD-block or K^+-sparing No (%)	332/8,407 (3.9)*
ACEI + ALD-block No (%)	209/332 (63)§
ACEI + K^+-sparing No (%)	123/332 (37)§

Over-65, individuals ≥ 65 year-old; M ± SD, mean ± standard deviation; M, male; F, female; No, number; %, percent; ACEI, angiotensin-converting enzyme inhibitor; ALD-block, aldosterone antagonist; K^+-sparing, potassium sparing diuretic (e.g. amiloride, potassium canreonate); *percent is related to 8,407 Emergency entries; §percent is related to 332 patients with heart failure.

Table 2: Characteristics of 5,755 over-65 patients with single or multiple Emergency admissions

Diagnosis at Emergency admission	No	(%)
Admissions with diagnosis presented in one or two patients only	147	44.3
Chest pain without MI	19	5.7
Pulmonary oedema, heart failure	19	5.7
Syncope	18	5.4
Flutter or atrial fibrillation	13	3.9
Respiratory failure	12	3.6
Low back pain	10	3
Pleural effusion	7	2.1
Acute exacerbation COPD	7	2.1
Hyperkalaemia	7	2.1
Nose bleeding	5	1.5
Stroke	5	1.5
Weakness	4	1.2
No diagnosis	5	1.5
Wrist fracture	4	1.2
Trauma	4	1.2
Angina pectoris	4	1.2
Head injury	3	0.9
Abdominal pain	3	0.9
Peripheral oedema	3	0.9
Renal colic	3	0.9
Acute renal failure	3	0.9
Urinary tract infection	3	0.9
Acute confusional state	3	0.9
Low blood pressure	3	0.9
Diabetic emergency	3	0.9
Lymphangitis	3	0.9
Pneumonia	3	0.9
Anuria	3	0.9
COPD	3	0.9
Bleeding	3	0.9

Over-65- individuals ≥ 65 year-old; ACEI- Angiotensin-Converting Enzyme Inhibitor; No- number; %: Percent; MI: Myocardial Infarction; COPD: Chronic Obstructive Pulmonary Disease

Table 3: Diagnosis at Emergency admission of 332 over-65 undergoing treatment with ACEI and aldosterone antagonist or potassium sparing diuretics.

Patient (No)	Age (years)	Sex (M/F)	PC	PMH	CKD	ACEI	ALD-block	K+-sparing
1	79	F	Acute confusional state	T2DM, CHD, HF, HYP, PM, HYPTH	Stage 3	Lisinopril 10 mg od	Spironolactone[a] 50 mg od	NP
2[b]	82	M	Syncope	T2DM, HYP, HF, Blindness	Stage 4	Ramipril 5mg od	NP	Amiloride[c] 5 mg od
3	77	F	Cachexia	CHD, HF, PM, AF	Stage 4[d] AKI	Perindopril 4 mg od	Spironolactone[a] 50 mg od	NP
4	74	F	Malaise	T2DM, HF	Stage 4	Lisinopril 10 mg od	Spironolactone[a] 50 mg od	NP
5	81	F	Chest pain	HYP, HF, AF, CD, T2DM, CLL	Stage 3[d] AKI	Ramipril 5 mg od	Spironolactone[a] 50 mg od	NP
6	82	F	Syncope	CD, HYP, HF, PM, HIPR	Stage 3[d] AKI	Ramipril 5 mg od	Spironolactone[a] 50 mg od	NP
7	79	M	Dyspnoea, peripheral oedema	HYP, HF, CHD, PE, CD	AKI	Lisinopril 10 mg od	Spironolactone[a] 50 mg od	NP

Over-65- individuals ≥ 65 year-old; ACEI: Angiotensin-Converting Enzyme Inhibitor; HF: Heart Failure; No: Number; M: Male; F: Female; PC: Present Complaint; PMH: Past Medical History; CKD: stage of Chronic Renal Disease at admission (eGFR calculated by http://www.mdrd.com); ALD-block- Aldosterone Antagonist; K+-sparing- potassium sparing diuretic; T2DM: type 2 Diabetes Mellitus; CHD: Coronary Heart Disease; CD: Cerebrovascular Disease; HYP: Arterial Hypertension; PM: Pace-Maker; HYPTH: Hyperthyroidism; NP: Not Prescribed; [a]Spirolactone was administrated in association to furosemine 20 mg; od: once daily; [b]this patient died before Hospital discharge and it couldn't be retrieved the cause of death; [c]Amiloride was administrated in association to hydrochlorothiazide; [d]about 1 month before admission; ARF: Acute Renal Failure at admission; AF: Atrial Fibrillation; AKI: Acute Kidney Injury; CLL: Chronic Lymphocytic Leukaemia; HIPR: Hip Replacement; PE: Pulmonary Embolism

Table 4: Over-65 HF Emergency admissions with serum potassium ≥ 6 mEq/l. Patients before entry were under treatment with angiotensin-converting enzyme inhibition and aldosterone antagonist or potassium sparing diuretics.

Patient	Before Emergency admission*		At Emergency admission		One day after Emergency admission		After Emergency admission**	
No	sCr	sK^+	sCr	sK^+	sCr	sK^+	sCr	sK^+
1	NA	NA	1.6	8.2	1.5	7.5	NA	NA
2[§]	NA	NA	2.5	7.9	2.1	7	NA	NA
3	1.4	5.9	8.9	6.3	7.8	5.1	1.4	3.9
4	NA	NA	1.7	7.9	NA	NA	1.5	4.3
5	1.4	4	2.2	6.9	2.3	5.4	1.1	5.4
6	1.1	3.7	2.2	7	1.7	5.2	1.1	3.9
7	NA	NA	2.9	8.5	2.6	8	NA	NA

Over-65- individuals ≥ 65 year-old; ACEI: Angiotensin-Converting Enzyme Inhibitor; *from 1 to 3 months before Emergency admission; **between 1 month and 1 year from Hospital discharge; sCr: serum creatinine (mg/dl); sK^+: serum potassium (mEq/l); NA: not available; [§]this patient died before Hospital discharge and it couldn't be retrieved the cause of death

Table 5: Laboratory findings of seven over-65 patients with serum potassium ≥ 6 mEq/l at Hospital admission. All patients were undergoing treatment with angiotensin-converting enzyme inhibition and aldosterone antagonist or potassium sparing diuretics.

our data (Table 1) ALD-block was underused even after the 1999 report of Pitt et al. [7], and still is [9,17] despite the ACC/AHA joint guidelines of 2005 and 2009 [10,11]. It could be related to either the ALD-block and hK^+ case reports [12] or the concern associated with the increasing number of patients with CKD.

In our 7 hK^+ cases (2.1%), 6 of them were under ACEI with ALD-block and 1 patient was treated with K^+-sparing. However, the main cause of hK^+ wasn't ALD-block but AKI. It should suggest the need for a closer clinical and laboratory follow-up of HF patients, particularly those with underlying CKD.

At least two weak points need to be acknowledged in this study. The main limitation is that this is an observational retrospective study without a case-control analysis. Additional limitation is due to DH since it was taken at the time of admission showing a 70% match with the Local Medical District database. Strength of this study might be in focusing on the association between hK^+ and the standard treatment for patients with HF. There is an apparent lack of documentation on the real impact that ACC/AHA guidelines [7,14,15] have on the general population. In conclusion, our analysis suggests that the safety of ACEI with ALD-block as standard treatment for HF, particularly in patients with underlying CKD, needs careful monitoring in order to avoid the development of AKI and hK^+.

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