ORIGINAL ARTICLE

Iatrogenic hyperkalemia as a serious problem in therapy of cardiovascular diseases in elderly patients

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KEY WORDS

cardiovascular diseases, elderly patients, iatrogenic hyperkalemia

ABSTRACT

INTRODUCTION The therapy of cardiovascular diseases has improved rapidly over the past 20 years. The most commonly used medications in cardiac patients are drugs affecting potassium homeostasis in the kidneys or the gastrointestinal tract, particularly inhibitors of renin–angiotensin–aldosterone (RAA) axis. They all can lead to hyperkalemia. This disorder may cause severe damage to the muscles and both the nervous and cardiovascular systems.

OBJECTIVES The aim of this study was to evaluate the incidence and clinical course of moderate and severe iatrogenic hiperkalemia in patients hospitalized for cardiovascular disease.

PATIENTS AND METHODS The present study analyzed a history of 26 patients with severe or moderate iatrogenic hyperkalemia, selected from among 5553 patients hospitalized in the years 2005–2006 in the Department of Clinical Cardiology of the Świętokrzyskie Cardiology Center, Kielce. They accounted for 0.46% of all patients treated at that time at the Ward.

RESULTS The concentration of potassium on admission to hospital was >6.0 mmol/l. Before admission all patients were treated in out-patient clinics with angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, spironolactone, amiloride, triam-terene, β-blockers, or potassium supplements administered in monotherapy or in combination. A mean age of patients was 79 years, most of them (80%) were women. The average blood potassium level was 7.3 mmol/l on admision and 5.1 mmol/l at discharge. Severe bradyarrhythmia and complete atrioventricular block requiring temporary pacing (n = 13) were observed in 21 patients (81%). Twenty-four patients (85%) had elevated levels of renal function parameters on admission. The average creatinine level on admission was 2.64 mg/dl, and 2.06 mg/dl on discharge. Ten (38%) out of 26 patients suffered from diabetes and 21 patients (81%) had arterial hypertension. Three out of 26 patients died in the hospital despite intensive therapy.

CONCLUSIONS Polypharmacy should be used with particular caution in subjects treated on the ambulatory basis. During administration of inhibitors of RAA system, particularly in elderly out patients, renal function and serum electrolytes should be appropriately monitored both prior to and during the treatment.

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INTRODUCTION Advances in pharmacotherapy of cardiovascular diseases in the last 20 years has led to a decrease in morbidity and mortality and improved quality of life in several patients worldwide. However, it has simultaneously resulted in an increase in the incidence of undesirable effects of therapy. One of these symptoms is iatrogenic hyperkalemia, a phenomenon which results from a common use of drugs interfering with potassium balance in the kidneys and gastrointestinal tract. Hyperkalemia is now a frequent cause of hospitalization of patients in departments of cardiology and in its severe form is life-theatening and associated with a 35–67% mortality.[1] Multicenter randomized clinical trials showed that angiotensin-converting enzyme inhibitors (ACEI),

angiotensin II receptor antagonists (ARA), mineralocorticoid receptor blockers (spironolactone, eplerenone), epithelial sodium channel (ENaC) inhibitors (amiloride, triamterene) are highly effective; renin inhibitors (aliskiren) are also used. These drugs, similar to β-adrenolytics or commonly used nonsteroidal anti-inflammatory drugs, predispose to hyperkalemia, and their common administration is supported with potassium supplementation. The therapy, especially in the case of insufficient monitoring or noncompliance may lead to severe iatrogenic hyperkalemia, especially in elderly patients, and those with renal insufficiency or other systemic diseases (i.e. neoplastic disease).

The aim of the study was to evaluate the frequency and clinical course of moderate and severe iatrogenic hyperkalemia in patients hospitalized in the years 2005–2006 in the 1st Clinical Department of Cardiology of the Świętokrzyski Cardiology Center (ŚCK) in Kielce.

PATIENTS AND METHODS The study was retrospective. All patients hospitalized in the years 2005–2006 in the 1st Clinical Department of Cardiology of the ŚCK with diagnosis of acute, severe or moderate iatrogenic hyperkalemia were evaluated. Hyperkalemia was defined as a plasma potassium level over 5.5 mmol/l. Mild (5.5–6.0 mmol/l), moderate (6.1–7.0 mmol/l) and severe (>7.0 mmol/l) hyperkalemia was distinguished.[2-4] We studied patients with moderate and severe hyperkalemia, with the potassium level on admission of >6 mmol/l, previously taking – in monotherapy or in combination – the following medications: ACEI, ARA, mineralocorticoid receptor blocker (spironolactone), ENaC channel inhibitors (amiloride, triamterene) and β-adrenolytics, or using potassium supplementation.

RESULTS In the years 2005–2006, in the 1st Clinical Department of Cardiology of the ŚCK, 5553 patients were hospitalized; in 26 subjects severe or moderate iatrogenic hyperkalemia was diagnosed; they represented 0.46% of all patients treated in this period. The mean age of the studied group was 79 years, with a predominance of women (81% of all patients) (TABLE). In 21 patients (81%) hypertension was diagnosed. Ten out of 26 patients (38%) hospitalized because of hyperkalemia suffered from diabetes, and 2 patients underwent one-sided nephrectomy (due to renal clear cell carcinoma). The history of ischemic heart disease was positive in 16 patients (62%), and 5 patients experienced myocardial infarction. All patients received ACEI, ARA, spironolactone derivatives, potassium and β-adrenolytics in monotherapy or in combination. An additional intake of nonsteroidal anti-inflammatory drugs predisposing to hyperkalemia in a substantial percentage of patients (35%) should be noted. However, the precise drug dosage could not be estimated due to memory disturbances and a poor general condition of patients, which often hamper communication. Almost all the patients reported fatigue, dyspnea and dizziness on admission; 81% reported loss of consciousness in the past. Paresthesia and decreased muscular strength were also reported. Disturbances of verbal contact, impaired consciousness and confusion were observed on initial examination. The mean blood potassium level measured on admission was 7.3 mmol/l and 5.1 mmol/l on discharge. In 21 patients (81%) atrioventricular (AV) conduction disturbances in the form of complete AV block were observed; 13 patients (50%) required temporary cardiac pacing; in the remaining patients conduction disturbances were transient and resolved after administration of 10% calcium gluconate, 20% glucose and insulin, and/or furosemide. Bradycardia and electrocardiogram (ECG) showing characteristics of hyperkalemia such as spiked T waves, flattening P waves, prolonged PR and widened QRS complex were observed in the remaining patients. None of the patients required permanent cardiac pacing. Increased creatinine levels were observed on admission in 22 patients (85%). However, the estimated glomerular filtration rate (eGFR) calculated using the Cockroft and Gault formula (TABLE) was decreased in all patients, i.e. eGFR of 30–59 ml/min/1.73 m^2 was found in 6 patients (23%), eGFR of 15–29 ml/min/1.73 m^2 in 16 patients (62%), and finally end-stage renal disease (eGFR <15 ml/min/1.73 m^2) in 4 patients (15%). A mean creatinine level on admission was 2.64 mg/dl and on discharge 2.06 mg/dl. All patients had clinical symptoms of left ventricular or biventricular heart failure in New York Heart Association (NYHA) class II–IV. Left ventricular ejection fraction on echocardiography in the study group was on average 45%. Three out of 26 hospitalized patients (12%) with end-stage renal disease and symptoms of advanced heart failure died. Water balance, blood pressure and the ECG recordings were monitored in all patients in the intensive cardiac care unit. Patient management included intravenous administration of calcium, glucose with insulin, administration of β-adrenolytics, sodium bicarbonate and ion-exchange resins; forced diuresis was also performed. Hemodialysis was necessary in 12 patients. We presented here 2 brief case reports, in which one patient recovered and the other died.

Case 1 An 89-year-old patient (No 829/05) with arterial hypertension, heart failure and a history of toxic nodular goiter, treated in the outpatient clinic with perindopril 5 mg/day, spironolactone 50 mg/day, potassium chloride 1 × 0.315 g, acetylsalicylic acid 1 × 0.075 g, thiamazole 15 mg/day, was admitted to the hospital because of atrioventricular conduction disturbances with bradycardia of 30/min. Her general condition was very poor, hypotonia was observed, the patient was agitated with no verbal and logical contact. Laboratory tests showed the hemoglobin level of 10.8 g/dl, white blood count of 13.1 G/l, urea of 242 mg/dl, creatinine of 3.44 mg/dl, sodium of

142 mmol/l, and potassium of 8.2 mmol/l. Third-degree atrioventricular block with ventricular escape rhythms of 30/min were observed on the ECG. Calcium gluconate 10%, sodium bicarbonate, glucose with insulin infusion, 0.5 mg of salbutamol intravenously, sodium polystyrene sulfonate per rectum and furosemide were administered; then hemodialysis was performed. Within the first 8 hours of hospitalization the patient required temporary cardiac pacing. The potassium level and renal function parameters simultaneously normalized. Atrioventricular conduction disturbances on the ECG resolved. On the 2nd day of hospital stay atrial fibrillation with an average ventricular rhythm of 144/min was observed. On the 3rd day of hospital stay a sudden cardiac arrest in the form of asystole occurred and hemodynamically effective heart function could not be restored despite attempts at resuscitation. The patient was pronounced dead.

Case 2 An 87-year-old patient (No 2620/05), with hypertension and ischemic heart disease, treated with amiloride + hydrochlorothiazide 0.005/0.05 g, potassium chloride 1 × 0.391 g was admitted to the hospital because of malaise and significantly reduced exercise tolerance for a few days prior to admission. The patient was in a severe condition, was apathetic with difficult communication. Laboratory tests showed the white blood cell count of 11.7 G/l, erythrocyte count of 3.88 T/l, urea of 113 mg/dl, creatinine of 2.61 mg/dl, sodium of 141 mmol/l and potassium of 10.0 mmol/l. On the ECG features of complete AV block with escape rhythm and widened QRS complexes with a heart rate of 40/min were shown. Calcium gluconate 10%, sodium bicarbonate, glucose with insulin infusion, 0.5 mg of salbutamol intravenously, and sodium polystyrene sulfonate per rectum were administered. On the 2nd day of hospitalization return of sinus rhythm with a heart rate of 99/min was observed on the ECG. The potassium level on the 2nd day of hospitalization decreased to 5.4 mmol/l. The patient's general condition gradually improved. On the 8th day of hospitalization the patient was discharged with a good general condition. Combined antihypertensive treatment with amlodypine in a dose of 5 mg/day and furosemide in a dose of 20 mg every other day with potassium supplementation under electrolyte check-up tests were recommended.

DISCUSSION Factors that predispose to hyperkalemia involve old age, progressing renal function impairment, heart failure, diabetes, an excessive potassium intake in food and an intake of drugs reducing renal potassium excretion.

Most of the body potassium (about 90% of 3500–4000 mmol, the whole body potassium pool) is localized in the extracellular space, including about 75% in muscles, and 7–8% in the liver and erythrocytes. Extracellular fluid contains about 10% of body potassium, where only 1% (15–25 mEq, that is 3.0–5.0 mmol/l) is directly located in plasma.[2,3] A daily potassium intake in food is 50–100 mmol, under physiological conditions 90% of potassium in food is excreted by the kidneys, and the remaining 10% – by the digestive tract. The main regulators of kalemia are the kidneys, digestive tract and transmembranal transport from extracellular to intracellular space and conversely. An intracellular potassium inflow is enhanced by such factors as insulin, aldosterone, β-adrenergic activity of the sympathetic system and alkalosis. A reverse effect is caused by deficiency of these hormones, β-adrenergic inhibition, acidosis and hyperosmolar plasma.[2,3] The kidneys play an important role in potassium homeostasis, providing excretion of the majority of this ion. The amount of excreted potassium results from glomerular filtration, tubular resorption and active excretion. Renal potassium excretion is decreased through reduced number of active nephrons, systemic acidosis and hyperkalemic forms of tubular acidosis, blockade of sodium channels (i.e. by triamterene or amiloride), states of aldosterone deficiency caused by renin deficiency induced by nonsteroidal anti-inflammatory drugs, ACEI, ARA, a class of mineralocorticoid receptor antagonists, e.g. spironolactone and eplerenone, decreased aldosterone and glucocorticoids (ketoconazole or heparin) synthesis.

Mild and moderate hyperkalemia are asymptomatic and can be diagnosed incidentally. Severe hyperkalemia gives rise to neuromuscular and cardiovascular symptoms.[4] These symptoms, including substantial weakness, paresthesia, muscular weakness and dizziness were observed in the study participants. Cardiac symptoms involve atrioventricular and intraventricular conduction disturbances, bradycardia, additional and characteristic changes of the repolarization period and P waves on the ECG. The earliest and the most characteristic abnormality observed in hyperkalemia on the ECG are spiked T waves. This symptom is related to action potential duration shortening as a result of acceleration of the fast repolarization phase. The change of T wave shape or their inversion and QT interval shortening appear at the serum potassium level of 5.5 mmol/l. QRS complexes widening, flattened P waves and prolonged PQ interval are observed at hyperkalemia of 5.5–7.5 mmol/l on the ECG. In advanced hyperkalemia, at the potassium level of >8.5 mmol/l, P waves can be invisible.[4,5] Secondary and tertiary centers, atrioventricular node, His-Purkinje system frequently take on the role of a leading pacemaker. Transient AV III° block was observed in 81% of the studied patients, but in 50% of subjects temporary pacing was required. A substantially increased potassium level may cause asystole or ventricular fibrillation and a cardiac arrest, which was observed in 3 patients despite the balanced plasma potassium level.[4,5]

In cases of mild hyperkalemia treatment modification aimed at renal function improvement,

discontinuation of potassium excretion inhibiting drugs, administration of a loop diuretic and appropriate patient hydration are usually sufficient. In the case of moderate and severe hyperkalemia, the patient needs hospitalization. Management of hyperkalemia comprises intravenous administration of calcium, glucose with insulin, β-agonists (i.e. salbutamol), sodium bicarbonate, oral or per rectum administration of ion-exchange resins and forced diuresis with loop diuretics. In the case of severe hyperkalemia and coexisting renal insufficiency hemodialysis is the preferred procedure. In the case of severe bradycardia, temporary transvenous cardiac pacing must be used. Despite the appropriate, as it seemed to be, management, mortality in the analyzed patient group with iatrogenic hyperkalemia was 12%. All study participants were taking drugs interfering at different levels with the renin–angiotensin–aldosterone system (RAA) in monotherapy or in combination.

In the last 2 decades a number of multicenter studies have been conducted, which showed the undisputable role of drugs inhibiting RAA system activity in decreasing cardiovascular mortality and morbidity. A multilevel blockade of the RAA system has become the standard of pharmacotherapy particularly in patients with severe heart failure and post-infarction myocardial injury. As previous reports on cardiovascular risk reduction and prognosis improvement in patients taking ACEI, ARA and aldosterone antagonists have been published, recommendations for their use were expanded. At present, therapy with ACEI has the highest class of recommendations – I, with an A level of evidence in patients with NYHA II–IV class heart failure and left ventricular ejection fraction ≤40%, regardless of symptoms, and in all patients following myocardial infarction, independent of the level of myocardial damage, especially if diabetes, left ventricular dysfunction and hypertension coexist.[6-10] ACEI and ARA are drugs of first choice in pharmacotherapy of hypertension, used also in patients >80 years.[11] Both ACEI and ARA may impair renal function, especially in patients with concurrent dysfunction of this organ, in old age, especially in the initial phase of the therapy.

Moreover, addition of other drugs interfering with the potassium balance (aldosterone antagonists, β-adrenolytics) is recommended depending on the class of heart failure or grade of hypertension. Add-on type trials, based on adding another drug to standard therapy, i.e. CHARM-Added, validate the use of ACEI combined with ARA.[12] The beneficial effects of combination therapy of ACEI and ARA in patients with advanced heart failure (class I recommendation, level of evidence B) and after myocardial infarction with symptomatic heart failure and left ventricular systolic dysfunction (EF <40%) (IIb/B) are more and more frequently stressed.[6,9] Finally, RALES and EPHESUS studies showed that diuretics – aldosterone antagonists, spironolactone and eplerenone derivatives added to conventional therapy in patients with advanced NYHA III–IV class heart failure and used in patients with post-infarction myocardial injury with ejection fraction of <40%, with concomitant heart failure or diabetes, significantly reduce mortality and the hospitalization rate.[13,14] After encouraging results from RALES and EPHESUS trials, this class of drugs was widely administered to patients with heart failure and following myocardial infarction (I/B). However, a higher prescription rate of aldosterone antagonists led to a 3–5-fold increase in the number of hospitalizations for hyperkalemia and a 2-fold increase in the number of hyperkalemia-related deaths.[1,15] It should be remembered that medications inhibiting the RAA system activity significantly decrease kaliuretic properties of diuretics and a daily intake of potassium in diet, estimated at about 100 mmol, may be sufficient to balance renal potassium loss resulting from the use of diuretics.[16] However, it frequently appears that administration of RAA system inhibiting drugs is accompanied by simultaneously prescribed potassium supplementation. In effect, in accordance with standards a patient obtains several drugs increasing the plasma potassium level. If the commonly used nonsteroidal anti-inflammatory drug and oral potassium supplementation are used in combination, the risk of iatrogenic hyperkalemia is significant. The results of the ONTARGET study, evaluating the effectiveness and safety of combined therapy of 10 mg of ramipril and 80 mg of telmisartan in a high cardiovascular risk group, showed a higher risk of hyperkalemia and combined therapy related occurrence of renal failure, and no superiority over ramipril in monotherapy. [17]

In the era of common polypharmacy it is extremely important to follow safety rules of RAA system interfering therapy rigorously, especially in elderly patients, patients taking nonsteroidal anti-inflammatory drugs, patients with diabetes and with impaired renal function. In this paper such patients experienced iatrogenic hyperkalemia. The serum creatinine level not always accurately reflects renal function. In such cases (especially in elderly patients) evaluation of creatinine clearance is recommended.

Contemporary standards of therapy with ACEI, ARA and aldosterone antagonists state that renal function and electrolyte levels should be evaluated prior to the therapy, low doses of drugs need to be used at the start of therapy and renal parameters and plasma potassium levels 1–2 weeks after introducing the therapy should be monitored.[6] The initial blood potassium level of >5 mmol/l and creatinine level of >2.5 mg/dl are contraindications to such therapy. Spironolactone (or eplerenone) should not be added if a patient receives a combined therapy of ACEI and ARA, potassium supplementation or other potassium-sparing drugs. Similarly, in patients treated with a combination of ACEI and aldosterone antagonist, ARA is contraindicated.[6] In the case of simultaneous

TABLE Characteristics of patients with iatrogenic hyperkalemia treated in the 1st Clinical Department of Cardiology in 2005–2006

Pts	Age	Sex	$creat_1$	$eGFR_1$	$creat_2$	$eGFR_2$	K+ on admission	K+ on discharge	EF (%)	Out-of-patient treatment	Diabetes
KA	79	M	1.61	37	1.4	42	6.9	5.3	50	ACEI, K	–
KT	86	M	3.04	18	2.8	19	6.3	5.0	35	ACEI, ARA, NSAIDS	–
GT	59	F	1.06	59	1.02	60	7.8	4.9	55	AM[a]	+
GF	64	F	2.06	24	1.8	27	6.2	5.4	60	ACEI	–
JH	74	F	2.27	20	2.0	23	8.0	5.3	40	AA, AM, NSAIDS, LBA	+
DM	81	M	1.87	31	1.6	36	7.9	5.2	35	ACEI, AA	–
CA	85	F	2.98	26	–	–	6.5	–	10	ACEI, K	+
ŚL	90	F	3.44	10	–	–	8.2	–	–	K[a]	–
CJ	87	F	2.61	14	1.9	20	10.0	5.3	45	ACEI, ARA, AA	–
RW	80	M	4.17	12	3.8	15	6.2	5.0	50	ACEI, K	–
KT	84	F	2.8	16	2.4	17	6.2	4.9	40	ACEI[a]	–
PS	84	M	2.65	21	2.4	23	6.0	5.0	50	ACEI, NSAIDS	–
KJ	76	F	1.56	29	1.3	35	6.1	4.8	60	AA, AM, NSAIDS, K	–
KZ	88	F	1.13	33	1.2	31	6.2	5.0	40	LBA, K, NSAIDS[a]	–
ŁJ	75	F	1.56	30	1.3	35	7.7	5.3	50	ACEI, AA, K	+
PR	72	F	2.99	16	2.01	24	6.2	5.4	45	ACEI, AA	+
LW	79	F	3.05	14	2.5	17	6.9	5.2	50	AA, K[a]	+
MW	77	F	2.72	16	2.05	42	7.3	5.3	55	ACEI	+
JA	79	F	5.54	8	–	–	6.8	–	–	NSAIDS, K[a]	–
KZ	77	F	3.31	14	2.8	16	8.0	5.3	45	AA, NSAIDS[a]	–
KA	79	F	2.6	17	2.2	20	9.0	5.0	30	ACEI, AM, NSAIDS	+
ZL	82	F	3.4	12	2.8	15	8.0	5.3	40	ACEI	–
MU	77	F	4.8	9	3.0	15	9.2	5.0	45	AA[a]	+
JM	80	F	2.5	17	2.3	19	7.0	4.8	50	ARA, K[a]	+
AB	81	F	1.8	23	1.6	27	6.8	4.9	55	AM, K, NSAIDS	–
KJ	80	F	1.06	40	1.2	35	8.0	5.0	50	ACEI	–

a medicine which was allegedly taken (based on empty packaging, relatives' account, medical recommendation card)

Abbreviations: AA – aldosterone antagonist, ACEI – angiotensin-converting enzyme inhibitor, AM – amiloride, ARA – angiotensin II receptor antagonist, $creat_1$ – creatinine level on admission, $creat_2$ – creatinine level on discharge, eGFR ml/min/1,73 m^2 (estimated glomerular filtration rate) – glomerular filtration measured according to the Cockroft and Gault formula[18], $eGFR_1$ – on admission, $eGFR_2$ – on discharge, K – potassium substitution, LBA – β-adrenolytics, NSAIDS – nonsteroidal anti-inflammatory drugs

administration of nonsteroidal anti-inflammatory drugs, an ACEI dose should be modified or such therapy should be discontinued. The creatinine level increase up to 50% compared to the initial value and to 3 mg/dl is acceptable. However, an increase in creatinine levels of >3.5 mg/dl and that in a potassium levels of >6 mmol/l are indications for discontinuation of therapy with ACEI.[6]

The phenomenon of insufficient control of the therapy with RAA system blocking drugs and an increase in the frequency of severe iatrogenic hyperkalemia cases is gradually spreading. In this situation one of the oldest principles of medicine, *primum non nocere*, is extremely important.

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