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RESEARCH ARTICLE

Hyperkalemia, self-medication, and over-the-counter drug usage in patients with cardiovascular disease in the perspective of polypragmasy

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Cardiovascular disease is a leading cause of death globally. 40 percent of the adult Romanian population is hypertensive, and only three out of seven patients are getting the appropriate treatment. Hyperkalemia is in a close relationship with certain cardiovascular diseases, although the influence of a certain medical treatment on hyperkalemia is not yet established. The aim of our study was to evaluate the pharmacotherapy of a group of patients with cardiovascular disease, representative for the adult population of our are and to analyze the administered drug therapy regarding polypragmasy (the concomitant usage of more than five different classes of substances), over-the-counter drugs and usage of drugs used without medical – physician prescribed - indication, and to evaluate serum potassium levels. The cross-sectional, observational, prospective, pharmaco-epidemiological study targets the observation, recording and analysis of 301 adult patients' pharmacotherapy and laboratory findings. Based on the demographic data we found that the study group is representative for the adult population of our region. Hypertension was observed in 173 cases, and more than 60 percent of the patients were older than 65 years of age. Other comorbidities, such as ischemic cardiac disease, heart failure, arrhythmias, other cardiovascular diseases as well as chronic kidney failure and diabetes mellitus were positively associated with hypertension. In 50.8 percent of the cases usage of drugs without prescription was present. Likewise, multiple drug combinations were frequent with high rates of polypragmasy. Multiple drug combinations were observed, and self-medication rates were very high, which should be reduced substantially to obtain a more successful pharmacotherapy and a reduced drug interaction-induced side effect.

Keywords: polypragmasy, self-medication, hyperkalemia, cardiovascular disease

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Introduction

Cardiovascular disease (CVD) is a global leading cause of death, which causes one third of all deaths. In the European Union, CVDs are the cause of death in 54% of the male and 43% of the female population, and represent the first major cause of deaths [1,2,3]. In Romania, the mortality rate of CVDs is 225-450/100.000 in case of men and 175-350/100.000 in women [4]. 40% of the adult Romanian population suffers from hypertension, with only 44% being aware of their condition, and only 39% with some form of treatment [5]. According to a local study, hypertension could be prevented, or hypertensive patients could benefit of a better control on their disease, if they would follow a proper daily diet [5]. In Europe, Romania is the fourth leading country regarding the mortality of CVDs [7,8].

Evaluation of CVDs through laboratory parameters represents a useful and quite pragmatic approach of clinicians in certain studies [9 ,10, 11, 12]. In the modern era, influenced by advertisements, patients could use certain drugs and supplements – without informing their attending physician – that could negatively influence their serum potassium levels, which can cause cardiac complications. The normal serum potassium level is 3.5 – 5 milliequivalents per liter (mEq/L). Hyperkalemia occurs when potassium levels are exceeding the high-end of the normal range, and it can be defined as mild (5.1 – 6.0 mEq/l), moderate (6.1 – 7.0 mEq/L) or severe (levels above 7 mEq/L) hyperkalemia. Major causes of hyperkalemia are kidney dysfunction, diseases of the adrenal gland and medication. [13, 14, 15]. Patients with kidney disfunction are especially sensitive to medications that increase blood potassium levels, and in certain cases both incorrect and correct administration of salt substitutes and/or potassium supplements can raise serum potassium levels [, 16].

Objectives

The aim of our study was to evaluate the pharmacotherapy of the adult population with CVD, and to analyze the administered drug therapy regarding polypragmasy (according to definition: the concomitant usage of more than five different classes of substances), over-the-counter (OTC) drugs and usage of drugs without indication, and to evaluate health condition by assessment of a laboratory parameter (serum potassium level).

Material and methods

Our cross-sectional, observational prospective and pharmaco-epidemiological study intended to evaluate the pharmacotherapy of 301 adult patients in ambulatory care setting of the Internal Medicine Clinic II, during April-October 2018 We obtained the approval of the Ethics Committee of the University of Medicine, Pharmacy Science and

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Technology Tg-Mures (50/07.03.2018). We studied the occurrence frequency and severity of hyperkalemia in case of different diagnoses, different types of treatment. Inclusion criteria were the following: adult (over 18 years of age) outpatient with the suspicion or diagnosis of CVD, from the cardiology-internal medicine ward. We analyzed the data of those patients who where cronically – for more than six weeks – receiving pharmacological treatment. The collected data were part of the routinely collected medical history and laboratory test results. The method used for serum potassium determination was ion selective electrode. Polypragmasy is defined as the concomitant usage of more than five different drugs. The statistical analysis was performed using Excel 2016, EpiInfo and GraphPad Prism 8 The threshold of significance was set to $p<0.05$.

Results

Hypertension was observed in 173 cases, of which 54.9% were male patients, and more than 60% were over 65 years old, 57.97± 17.60. The most often diagnosed diseases were ischemic cardiopathy (78.0%), heart failure (62.4%), hypertension (57.5%), other cardiovascular diseases (different types of cardiomyopathies, 47.4%), arrhythmias (46.2%), and comorbidities such as chronic renal failure (23.7%) and diabetes mellitus (34.7%).

Evaluation of potassemia was performed in every case of these medical conditions. We observed that serum potassium level measurement was requested by the attending physician for each case, although this was not a criterium to include them in our study. In 82.1% of all cases, we found hyperpotassemia.

We evaluated the occurrence of hyperpotassemia in different cardiovascular diseases. The results are similar in each case of associated CVDs. After performing the statistical analyses, we found a statistically significant relationship ($p=0.0119$) in case of patients with chronic renal failure, confirming the risk for the development of abnormal serum potassium levels in these patients.

To complete the evaluation of hyperpotassemia, we analyzed it based on its severity, the results are included in the Table I and II.

The study showed, that only 17.9% of the subjects had normal serum potassium levels, and the authors identified two cases with extremely high serum potassium levels (>7 mEq/l).

Self-medication and OTC drugs have also been evaluated, as these can contribute to the development of certain symptoms due to drug interactions (Table III).

Important to take into consideration is the frequent use ofnon-steroidal anti-inflammatory drugs, as over-the-counter medications, a group with high protein plasma binding character, responsible for many drug interactions. In 50.8% of cases self-medication and usage of over-the-counter medications, drugs occurred.

Multiple drug combinations were also frequently present in our study group, as well as polypragmasy, which was present in more than half of the cases. In almost 10% of our subjects, more than 10 different types of drugs were used concomitantly.

Table I. Frequency of hyperpotassemia in different CVDs

Diagnosis	Number of cases	Percentage
Hypertension		
Normal potassium level	29	16.8%
Hyperpotassemia	144	83.2%
Ischemic heart disease		
Normal potassium level	28	15.0%
Hyperpotassemia	159	85.0%
Heart failure		
Normal potassium level	27	16.0%
Hyperpotassemia	142	84%
Other cardiovascular diseases		
Normal potassium level	18	12.2%
Hyperpotassemia	129	87.8%
Arrhythmia		
Normal potassium level	17	12.7%
Hyperpotassemia	117	87.3%

Table II. Severity of hyperpotassemia

Serum potassium levels	Cases	Percentage
3.5 – 5.0 mEq/L	54	17.9%
5.1 – 6.4 mEq/L	225	74.8%
6.5 – 8 mEq/L	20	6.6%
>8 mEq/L	2	0.7%
Total	301	100%

Table III. Most frequently administered drugs

Drug	Cases	Percentage
Amiodarone	32	10.6%
Antiaggregants	132	43.9%
Anticoagulant - Acenocumarol	132	43.9%
Non-selective beta blockers	9	3.0%
Selective beta blockers	106	35.2%
Digoxin	61	20.3%
Diuretics - NPS	194	64.5%
Diuretics – PS (Spironolactone)	157	52.2%
Gastrointestinal drugs	137	45.5%
Hypolipemiant drugs	53	17.6%
ACE Inhibitors	168	55.8%
Nitrates	44	14.6%
Calcium channel blockers - DHP	47	15.6%
Non DHP - Verapamil	23	7.6%
NSAID	84	27.9%
Bronchodilators	110	36.5%
Sedatohypnotics	67	22.3%
Vasodilators	30	10.0%

Discussion

Self-medication is a general tendency in our modern society. Polypragmasy – a combination of more than five, and especially more than ten drugs - can be confusing for patients, increasing the risk of inappropriate dosages and mistakes. Coadministration of drugs, either different dosage forms or combined preparation with more than one active substance can lead to appearance of unwanted – rarely

wanted, synergistic interactions. Drug interactions can occur either via pharmacokinetic or pharmacodynamic ways of action. Absorption, biotransformation, elimination can be affected, leading to decrease or increase of the effect. Antagonistic drug interaction also modify the efficacy, causing dose-increase which additionally also causes more severe adverse effects. This variety of interaction possibilities makes the request for monitoring therapies from clinical pharmacological point of view even more important. Some drugs might be pro-oxidants, increasing the level of oxidative stress, causing damage to macromolecules [17]. Side-effects, like hyperpotassemia, might occur frequently in case of combinations of multiple drugs.

Education of the population, providing practical information, would be necessary not only regarding the risk of improper diet and unhealthy lifestyle habits [18], but is also essential regarding inappropriate medication use.

A potential risk of hyperkalemia in our study group is due to the administration of the potassium-sparing diuretic spironolactone. This drug is blocking the apical sodium channel of the collecting duct in the kidneys, and therefore decreasing the K^+ ion secretion into the lumen, leading to hyperkalemia [19].

Other drugs that can be a possible cause of elevated serum potassium levels are ACE inhibitors. The mechanism through which they produce this potential side effect is through the decreased concentration of angiotensin II (ATII), leading to aldosterone secretion in the zona glomerulosa of the adrenal cortex. The cellular membrane density of the Na^+ permease enzyme is increased through the more intense action of aldosterone, leading to an inflow of sodium into the renal tubular cell, inducing the transfer of this ion into the peritubular space through the increased activity of Na^+/K^+-ATPase on the peritubular side of the cell. Therefore, increased serum potassium concentrations can occur more frequently in patients with chronic kidney disease and in those who use K^+ sparing diuretics in combination, salt substitutions or have a diet with higher potassium content [20, 21, 22].

Another important class of substances related to hyperkalemia, used frequently by patients, even without any indication and without prescription by a healthcare professional, are non-steroidal anti-inflammatory drugs (NSAIDs). These drugs increase serum potassium concentration through the inhibition of prostaglandin stimulation of K^+-excretion in the collecting duct, and through the inhibition of renin release [19].

Conclusions

Based on our results it could be observed that our study group is representative for the adult population of our region. The frequency of hypertension is similar to the data from the international medical literature, with increasing frequency among the younger generations as well. The rate of multiple drug therapy and self-medication is high. The high frequency of polypragmasy is a major concern, and its reduction is highly recommended, based on the clinical pharmacology guidelines, in order to lower the risk of drug interaction-induced adverse reactions.

We observed that hyperpotassemia is present frequently in case of cardiovascular diseases and furthermore it is routinely evaluated by physicians. This increase of potassium concentrations is probably due to the high number of pharmaceutical combinations and to the underlying disease.

The analysis of the relationship between the main illness and appearance of hyperkalemia showed that chronic renal failure is a risk factor for developing increased serum potassium levels. We have also observed some interactions between this parameter and the administered therapy – an issue that will be the objective of our further research.

Authors' contribution

EGB and ZSS - Study protocol, Data collection, Data analysis, Literature review.
EADN and PL - Data analysis, Literature review.

Conflict of interest

None to declare.

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