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EVALUAREA COMPARATIVĂ A BIODISPONIBILITĂȚII PREPARATELOR PERORALE CU CONȚINUT DE POTASIU ȘI SPIRONOLACTONĂ

COMPARATIVE EVALUATION OF THE BIOAVAILABILITY FOR ORAL MEDICINES WITH POTASSIUM AND SPIRONOLACTONE

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Rezumat. Conform studiilor recente, una dintre cele mai răspândite cauzele a hipertensiunii arteriale este un consum ridicat de sare (clorură de sodiu) și un aport scăzut de potasiu (K+). Creșterea aportului de potasiu de 1,64 g poate reduce riscul de accident vascular cerebral cu 21% (p = 0,0007) și a bolilor cardiovasculare. În Republica Moldova există produse medicinale cu diferitele săruri de K+ care pot fi utilizate ca supliment mineral pentru tratarea deficienței de K+ (hipopotasemie). Astfel, a fost necesar să se stabilească unor parametri pentru a elabora medicamentul cu cea mai înaltă biodisponibilitate. Datele obținute vor fi utilizate pentru a selecta compoziția produsului medicamentos combinat cu cea mai mare biodisponibilitate, eficacitate și siguranță.
Cuvinte cheie: HIPOPOTASEMIE, POTASIU, SPIRONOLACTONE, ASPARTAT DE POTASIU, BIODISPONIBILITATE
Summary. According to recent studies, one of the widely-spread causes of the arterial hypertension is a high consumption of salt (sodium chloride) and a low potassium (K^+) intake. An increase in potassium intake of 1.64 g may reduce the risk of stroke by 21% (p=0.0007) and cardiovascular disease. There were found the different salts of K^+, which can be used as a mineral supplement to treat K^+-deficiency (hypopotassemia) in the Republic of Moldova. Thus, it was necessary to establish some parameters in order to find the medicine with the highest bioavailability. The obtained data will be used in order to select the composition to create the fixed-dose drug combination with the highest bioavailability, efficacy and safety.
Keywords: HYPOPOTASSEMIA, POTASSIUM, SPIRONOLACTONE, POTASSIUM ASPARTATE, BIOAVAILABILITY

INTRODUCTION

Arterial hypertension (AH) is a major public health problem due to its high prevalence all around the globe [1, 2, 3, 4]. Around 7.5 million deaths or 12.8% of the total of all annual deaths worldwide occur due to high blood pressure [5].

According to the obtained data from National Bank of Statistics of the Republic of Moldova it was established 23 386 deaths caused by cardiovascular disease (CVD) in the Republic of Moldova [6]. High blood pressure is the cause of about 62% of strokes and 49% of acute heart events, complications that could be prevented by proper blood pressure control. [7]. Arterial hypertension is a major risk factor for cardiovascular disease (CVD), including stroke, heart attack, heart and kidney failure, and aneurysm. More than one billion adults worldwide have hypertension with up to 45% of the adult populace being affected with the disease [8]. Recent estimates have suggested the number of patients with hypertension could increase as much as by 15 to 20%, which could reach close to 1.5 billion adults with AH by 2025 [9].

It is well-known relationship between AH and highly sodium intake. According to recent studies, one of the widely-spread causes of the AH is a high consumption of salt (sodium chloride) and a low potassium (K^+) consumption. Therefore, the World Health Organization (WHO) currently recommends for adults a consumption not higher than 5 g of potassium salt daily [10]. The ratio of sodium and potassium in the urine in AH exceeds 5.7 [11]. Unlike sodium, potassium increases blood flow and promotes vasodilatation as a result of hyperpolarization of vascular smooth muscle cell membranes by activation of Na^+/K^+ - ATP-ase and potassium channels. K^+ ions are also released by endothelial cells in response to neurohumoral mediators and

contribute to the process of endothelium-dependent vascular relaxation, being a component of endothelium-derived hyperpolarization factor-mediated responses [12, 13].

Moderate intake of potassium with food reach in K^+ or over-the-counter medicines (OTC) can lead to decrease in blood pressure (BP) in individuals with hypertension, especially in the absence of drug therapy. In contrast to sodium, dietary potassium has beneficial effects on BP and cardiovascular health [14, 15, 16]. An increase in potassium intake of 1.64 g may reduce the risk of stroke by 21% (p=0.0007) and CVD in general. Increasing the concentration of potassium in the blood plasma improves ventricular repolarization and reduces the risk of arrhythmia in patients with hypertension taking non-potassium-sparing diuretics, which can disrupt glucose tolerance and increase the risk of developing type 2 diabetes mellitus (DM2) by reducing insulin secretion in response to glucose loading [17, 18]. The administration of potassium supplements with thiazide diuretics avoids impaired insulin secretion in response to glucose loading [19].

Most patients with AH are effectively treated with diuretics. Antihypertensive therapy with diuretics such as loop (furosemide, torasemide, ethacrynic acid) and thiazides (hydrochlorothiazide, indapamide) lead to electrolyte abnormalities in particularly hypopotassemia. Hypopotassemia is present in up to 20% of hospitalized patients, 40% of patients taking diuretics, and 17% of patients with cardiovascular conditions [20]. Because loop and thiazide diuretics increase sodium delivery to the distal segment of the distal tubule, this increases potassium loss (potentially causing hypopotassemia) because the increase in distal tubular sodium concentration stimulates the aldosterone-sensitive sodium pump to increase sodium reabsorption in exchange for potassium and hydrogen ion, which are lost to the urine. The increased hydrogen ion loss can lead to metabolic alkalosis [21].

Unlike loop and thiazide diuretics, potassium-sparing diuretics (spironolactone) inhibit the actions of aldosterone (aldosterone receptor antagonists) at the distal segment of the distal tubule, therefore less potassium and hydrogen are lost to the urine [21]. Thus, potassium-sparing diuretics do not produce hypopotassemia as the loop and thiazide diuretics. Due to this they are called potassium-sparing diuretics and are widely-spread in medical practice.

Dietary supplementation of potassium can lower blood pressure in normal and some hypertensive patients. Again, in contrast to NaCl restriction, the response to potassium supplementation is slow to appear, taking approximately 4 weeks. Such supplementation reduces the need for antihypertensive medicines. "Salt-sensitive" hypertension responds particularly well, perhaps, in part, because supplementation with potassium increases the urinary excretion of sodium chloride. Potassium supplementation may even reduce organ system complications (e.g., stroke) [22].

The use of moderate doses of potassium with food does not cause severe hyperpotassemia or deterioration of kidney function in people with normal kidney function, even against the background of renin-angiotensin-aldosterone system blockers. Special care should be taken only in patients with severe renal impairment [23]. Increased potassium intake is recommended for patients without impaired renal potassium metabolism to control elevated blood pressure and prevent stroke [24, 25].

Due to intensive development of the pharmaceutical industry, there is a great variety of medicines reach in potassium salt for oral administration. The absence of domestic effective product for the correction of potassium deficiency is disappointing. From a pharmacoeconomical point of view, they are planned to be more affordable than foreign analogues for patients. Due to this, it could provide people with the most efficient and least expensive medicines. At the same time, it had to lead to efficient health care and had to improve the quality of an individual's life. Therefore, the creation of domestic effective products containing potassium is very actual and important aim for our country. Consequently, this product has to comply with high bioavailability and good tolerability with long-term use.

MATERIAL AND METHODS

It was applied the widely complex study of using the next databases: PubMed, Medline, Scopus, HINARI, SciSearch © The Thomson Corporation. In this present work 32 articles were analyzed. It was found the different salt of potassium, which is a source of potassium and is used as a mineral supplement to treat potassium deficiency. They are used as a transporter that carries potassium into the cells. According to the Nomenclature of the Republic of Moldova (RM), potassium medicines and supplement used to prevent and to treat low potassium is found in the various form of salts, such as: chlorides, aspartate, orotate and others, as noted in table 1.

Due to the different route of administration and the dose of medicine, they can be used in patients with hypopotassemia on the different levels. Hypopotassemia is classified as mild (serum potassium, greater than 3 to 3.5 mEq/L), moderate (serum potassium, 2.5 to 3 mEq/L), or severe (serum potassium, less than 2.5 mEq/L) [26]. Most cases of mild-to-moderate hypopotassemia may be corrected with oral potassium supplements and medicines (table 1).

Potassium chloride is should be given by intravenous route strictly, because large amounts for long-term administration cause damage to the small intestine, where absorption occurs 90% potassium. Potassium iodide is used as a source of Iodine (I_2) and as a mineral supplement to prevent and to treat I_2 deficiency. In addition, potassium iodide can block absorption of radioactive iodine by the thyroid gland through flooding the thyroid with non-radioactive iodine and preventing intake of radioactive molecules, thereby protecting the thyroid from cancer causing radiation. Moreover, salt iodization is the preferred policy to prevent iodine deficiency and associated disorders in the Republic of Moldova, due to nuclear accident that occurred in the North of Ukraine, Chernobyl. [27].

Table 1. Oral potassium medicines and supplement used in the different salts

Medicine name	Potassium salt	Pharmaceutical form	Potassium salt dose	Elemental Potassium dose
Iodomarin	Potassium Iodide	tablet	100 µcg 200 µcg	23 µcg 47 µcg
Panangin	Potassium Aspartate Magnesium Aspartate	tablet	158 mg 140 mg	36 mg (0.92 mEq)
Panangin® Forte	Potassium Aspartate Magnesium Aspartate	tablet	316 mg 280 mg	72 mg (1.8 mEq)
Miostenil	Potassium Aspartate Magnesium Aspartate	tablet	250 mg 250 mg	57 mg (1.45 mEq)
Potassium orotate	Potassium Orotate	tablet	500mg	100 mg (2.5 mEq)
KCl	Potassium Chloride	tablet retard	750mg 1000mg 1500mg	393mg (10 mEq) 524mg (13.4 mEq) 786mg (20.1 mEq)
Kalinor	Potassium Citrate monohydrate Potassium Hydrocarbonate	tablet efferv.	2170mg 2057mg	246mg (6.3 mEq) 803mg (20.5 mEq)

Potassium aspartate is active in the form of the levorotatory stereoisomer compared to dextrorotatory. It was proved by clinical trials in patients receiving furosemide and digoxin concomitantly. They were provided for 14 days with L-aspartic acid potassium and magnesium salt (K-Mg L-aspartate), D-aspartic acid potassium and magnesium salt (K-Mg-D-aspartate) and DL-aspartic acid potassium and magnesium salt (K-Mg-DL-aspartate). Applying atomic emission spectroscopy to analyze the blood, it was shown that L-aspartic acid potassium and magnesium salt compensated the most for the potassium deficiency compared to other aspartate stereoisomers [28].

Thus, various salt of potassium for oral route of administration have the different rate and active fraction of the initial dose of a medicine that successfully reaches the systemic circulation in a chemically unchanged form (bioavailability). Bioavailability, the "term" used is "F", is defined as the active fraction of drug from its pharmaceutical dosage form administered that gains access to the central circulation, i.e., the circulating post-portal venous blood. Bioavailability, F, refers to the extent a substance or medicine becomes completely available to its intended biological destination. More accurately, F is a measure of the rate and fraction of the initial dose of a drug that successfully reaches either; the site of action or the bodily fluid domain from which the medicine's intended targets have unimpeded access [29, 30, 31]. Therefore, F for a medicine administered intravenously is 100%. An F of 1.00 is equivalent to a bioavailability of 100%. Unlikely IV, just a part of a dose administered orally is "available" to the target sites of action. It is due to the number of factors, such as: the passage through the gastrointestinal (GI) system and hepatic first-pass metabolism. Therefore, the influence of oral pharmaceutical form on medicine's bioavailability is generally in the following order: Solution > Emulsion > Suspension > Powder > Capsule > Tablet [32].

It was applied a Lipinski Rule of Five states, which is used in order for the medicine to be orally active it must have: Not more than 5 hydrogen bond donors (OH and NH groups); Not more than 10 hydrogen bond acceptors (notably N and 0); A molecular weight under 500 g/mol; A partition coefficient log P less than 5. Therefore, the different salt of potassium used in hypopotassemia have been analyzed, as noted in table 2.

F is usually assessed by determining the area under the plasma concentration–time curve, as noted in figure. By plotting plasma concentrations of the medicine versus time, we can measure the area-under-the-curve (AUC). This curve reflects the extent of the medicine absorption. F of the medicine administered orally is the ratio of the area calculated for oral administration compared with the area calculated for IV injection (as noted in equation 1).

Table 2. Characteristic values of medicines used in hypopotassemia

Name Value	K^+Aspartate	K^+Orotate	K^+ Chloride	K^+Citrate	K^+Bicar-bonate	Spirono-lactone
Molecular Weight, g/mol	209.28	194.19	74.55	306.39	100.115	416.6
Hydrogen Bond Donor Count	1	2	0	1	1	0
Hydrogen Bond Acceptor Count	5	4	1	7	3	5
Rotatable Bond Count	1	1	0	2	0	2
Topological Polar Surface Area	106 Å²	98.3 Å²	0 Å²	141 Å²	60.4 Å²	85.7Å²
Formal Charge	0	0	0	0	0	0
Defined Atom Stereocenter Count	1	0	0	0	0	7
Covalently-Bonded Unit Count	3	2	2	4	2	1

Note: Data deposited in or computed by PubChem < https://pubchem.ncbi.nlm.nih.gov *>*

$$F = (AUC_{oral} / AUCparenteral) * 100\% \quad (1)$$

Key measurements are examined: $AUC_{(0\text{-last})}$ is defined as the area under the concentration-time curve from dosing (time 0) to the time of the last measured concentration; Maximum concentration (C_{max}) is defined as the maximum observed medicinal concentration observed in the blood, reported in units of ng/mL; Time of maximum concentration (t_{max}) is defined as the time at which the Cmax occurs, reported in units of h. AUC is directly proportional to the total amount of unchanged drug that reaches systemic circulation [30].

Plasma drug concentration increases with extent of absorption; the maximum (peak) plasma concentration is reached when drug elimination rate equals absorption rate. Bioavailability determinations based on the peak plasma concentration can be misleading because drug elimination begins as soon as the drug enters the bloodstream. It has been established that 10% of the dose of the potassium orotate taken orally is absorbed. It is converted into orotidine-5-phosphate in the liver and is excreted in the urine (30% as metabolites). The main route of elimination of potassium aspartate is renal (about 90% of potassium is excreted by the kidneys daily). The remaining 10% are excreted through the digestive tract.

Diuretic use is a common cause of renally mediated hypopotassemia [33]. The widely spread using of the diuretics such as loop (furosemide, torasemide, ethacrynic acid) and thiazides (hydrochlorothiazide, indapamide) is more likely to induce hypopotassemia than spironolactone. Unlikely loop and thiazide diuretics, spironolactone is potassium-sparing diuretics that blocks the aldosterone receptors due to similar chemical structure with aldosterone. Thus, it helps make more urine and to lose excess water from the human body with less K^+ lost to the urine [21].

Recently, it was demonstrated that after a single oral dose of spironolactone, 7 alpha-thiomethylspirolactone is the main metabolite and that unchanged spironolactone reaches maximum serum concentrations which are in the same order of magnitude as canrenone (see figure 2) [34]. Both spironolactone and 7 alpha-thiomethylspirolactone are known to possess anti-mineralocorticoid activity, and they may be mainly responsible for the activity of spironolactone. The uptake from the gastrointestinal tract is at least 70%. The protein binding averages 98%. The half-life is 18 to 20h after doses of 100 to 400m.g. It is eliminated as metabolites via the urine and the bile.

RESULTS AND DISCUSSIONS

The last few decades have witnessed an increase of importance of medicines bioavailability. It was shown that aspartate and orotate of potassium salt are more efficient than other in oral pharmaceutical form. First of all, these organic salts play some important roles: as a source of potassium and as a transporter that carry potassium into the cells, and other benefits are specific for these acids.

Thus, orotic acid exhibits antioxidant properties, since it is a key intermediate in the biosynthetic pathway of pyrimidines that promotes the synthesis of enzymes which act as free radical scavengers. Also, aspartic acid serves as a neurotransmitter and takes a part in the synthesis of other amino acids (Arginine, Lysine, Methionine, Isoleucine) and some nucleotides. It was established, that the L-aspartic acid potassium salt is the more bioactive form than its dextrorotatory stereoisomers. Due to combination with spironolactone (potassium-sparing diuretic), it could achieve the successful result in patient with hypopotassemia. Therefore, the creation of domestic effective medicines with the salt of potassium and spironolactone for the correction of potassium deficiency, which have high bioavailability and good tolerability with long-term use, is an urgent problem.

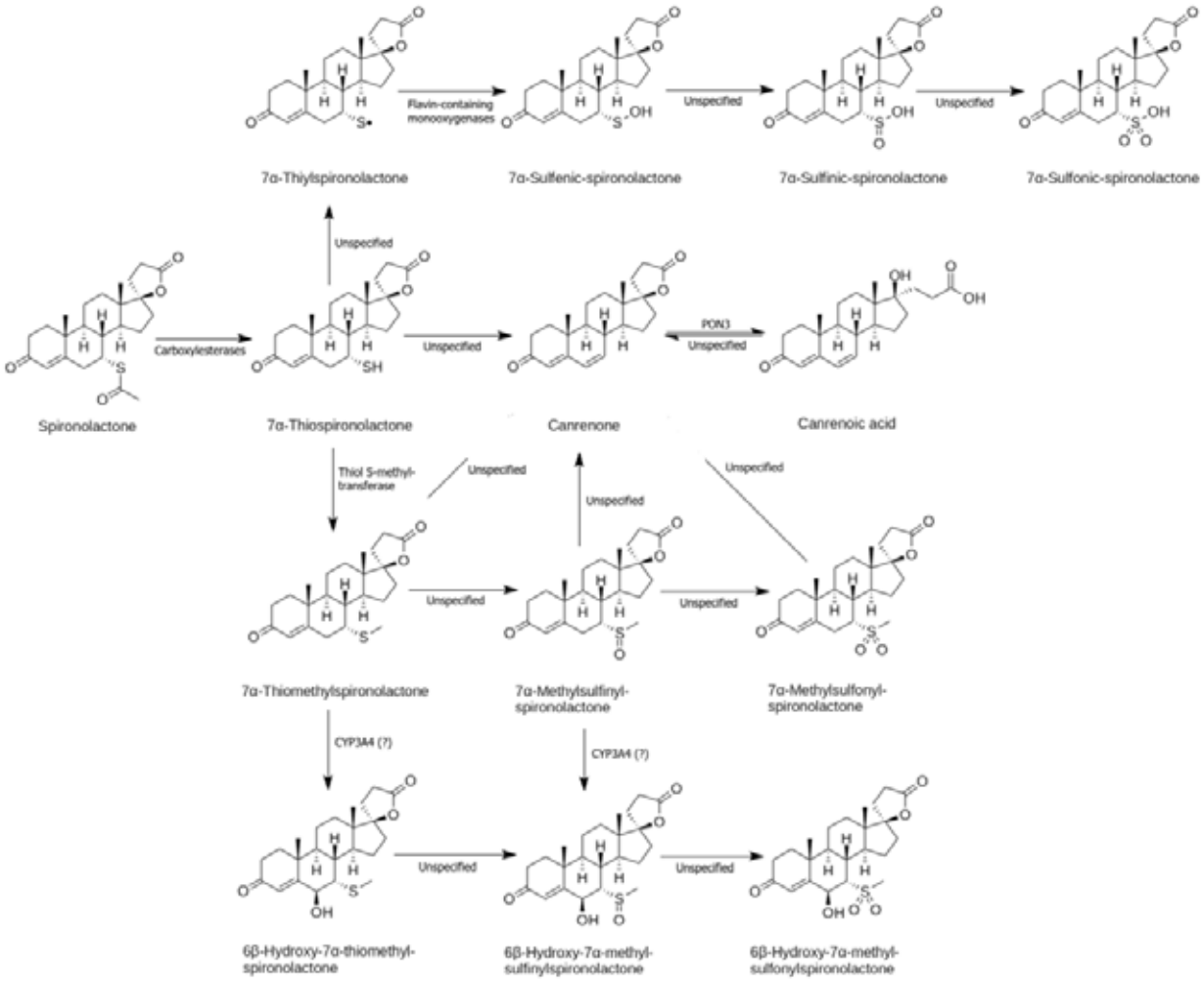

Figura 1. Spironolactone metabolism in humans.

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