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Original Study

Drug Sodium Intake - Warning in Cardiovascular Diseases Treatment

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SUMMARY

Introduction: Hypertension is a condition which represents one of the main risk factors for the development of cardiovascular diseases. High sodium intake contributes to occurrence of hypertension, increasing the volume of extracellular fluid. Therefore, World Health Organization (WHO) and other associations involved with hypertension research advise to decrease intake of sodium. Effervescent dosage forms usually contain high levels of sodium which could lead to above mentioned health issues.
Aim: The aim of this study was to evaluate the levels of sodium in the effervescent dosage forms available in the Serbian drug market.
Methods: Data about sodium levels, and excipients was obtained from Summary of Product Characteristics from website of Medicines and Medical Devices Agency of Serbia (ALIMS). Maximum daily doses recommended by the manufacturer and approved by ALIMS were observed. Exposure to sodium through consumption of maximum daily doses was calculated as percentages of the adequate daily intake given by Food and Nutrition Board (Institute of Medicine, National Academies, Washington D.C., USA), and also as percentage of recommended daily intake of sodium given by WHO.
Results: There are five formulations with exposure to sodium through consumption of maximum daily doses higher than 100% of the adequate daily intake (2 g), all of which are effervescent tablet formulations. The highest exposure to sodium was found in effervescent tablets containing acetylsalycic acid (500 mg) as active pharmaceutical ingredient: 250.62 % for people aged 51 to 70 years; 271.50 % for people aged 70 and older.
Conclusion: In effervescent dosage forms available on Serbian market, level of sodium can be very high, even up to 271.50% of adequate daily intake when maximum daily doses are consumed. Major cause for concern is for vascular patients who use effervescents for chronic therapy. This data should be considered during prescribing and dispensing this category of medicines as well as during analyzing pharmacovigilance.

Keywords: sodium content, hypertension, vascular therapy

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INTRODUCTION

Hypertension is a condition which represents one of the main risk factors for the development of vascular diseases especially cardiovascular diseases (CVD). Nowadays, CVDs are the most common cause of death. More than one in five adults have high blood pressure (1.13 billion people in the World) [1]. In Serbia, a study has found that 47% of adult population suffers from hypertension [2].

It is known that high intake of sodium contributes to occurrence of hypertension, increasing the volume of extracellular fluid [1,3]. Study has found that in 2010, 1.65 million deaths caused by cardiovascular complications were due to sodium consumption above 2 g per day [4]. Therefore, World Health Organization (WHO) and other associations involved with hypertension research advise decreased intake of sodium in all age categories. WHO gives recommended daily sodium intake (RDI) of 2 g per day [5]. American Food and Nutrition Board (Institute of Medicine, National Academies, Washington D.C., USA) developed Adequate Intake (AI) in different age groups, because they consider there is lack of scientific data needed to give Recommended Dietary Allowances (defined as an average daily dietary intake level sufficient to meet the nutrient requirements of 97–98% healthy individuals in a group) [6]. However, O'Donnell et al (2015) have challenged these guidelines, stating that people on low sodium diets (less than 3 g per day) have increased risk of cardiovascular complications over people with moderate sodium intake. They also question feasability of lowering sodium intake below 2 g per day, as there is yet no country in which these levels of sodium have been achieved [7]. Although the negative influence of sodium on health is known, it is used in medicine formulation as ingredient with many different functions. Sodium can be an active pharmaceutical ingredient (API) itself, however it is primarily an ingredient for increase of solubility of APIs as well as excipients. Functional categories of sodium-containing excipients include: disintegrant, chelating agent, lubricant, binder, emulsifier, stabilizing agent, dye, preservative and other [8].

Effervescent dosage forms contain sodium bicarbonate and sodium carbonate which combined with acidic agents in water produce carbon dioxide. These dosage forms usually contain high levels of sodium which could lead to health issues. However, effervescent dosage forms (tablets, granules and powders) have high compliance by patients. Studies that investigated reasons for better acceptance of these dosage forms have shown: preference over oral tablets and capsules due to swallowing difficulties; additional convenience for patients with gastrointestinal reflux (effervescents have buffering properties); pleasant taste; impression of faster therapeutic action [9].

All excipients which can cause adverse drug reactions are recognized as excipients with known effect (EKE) by regulatory bodies. There are rules about EKE labeling for outer and inner packaging and Summary of Product Characteristics (SmPC) with aim to inform health professionals and patients about potential risks associated with consumption of these medicines [10]. European Commission issued guidelines stating that sodium content must be listed for medicines that contain 1mmol or more sodium per dose [11]. European Medicines Agency (EMA) has established a limit – 17 mmol (391 mg) of sodium in maximum daily dose as acceptable [8].

AIM

The aim of this study was to evaluate the levels of sodium in the effervescent dosage forms available on the Serbian drug market.

METHODS

In this academic qualitative research we analyzed SmPC of effervescent dosage forms approved by ALIMS. SmPC document were taken from official website of ALIMS. Data about sodium content was found in sections 2. Qualitative and quantitative composition, 4.4. Special warnings and precautions for use and 6.1. List of excipients. Maximum daily doses recommended by the manufacturer and approved by ALIMS were observed in section 4.2. Dosage and method of administration [12]. Sodium content in maximum daily dose was calculated for each analyzed medicine.

Data about AI of sodium was obtained from official website of American Food and Nutrition Board (Institute of Medicine, National Academies) [6]. AI for children aged

1-3 years is 1 g; for children aged 4-8 years is 1.2 g; for people aged 9-50 years is 1.5 g; for people aged 50-70 years is 1.3 g; and for elderly over 70 years of age, AI is 1.2 g. Also, WHO's RDI of sodium for adults of 2 g per day was considered. WHO also states that RDI of sodium for children should be 2 g per day adjusted based on energy requirements, which is why no further calculations for children were done [5]. Exposure to sodium through consumption of maximum daily doses for each age group was calculated as percentages of the AI and also as percentage RDI given by WHO.

Also, data about sodium containing excipients present in analyzed medicines was obtained from SmPC document, section 6.1. List of excipients [12]. Percentage of analyzed formulations in which particular excipient is present was calculated for each sodium containing excipient. Chemical structures of excipients were made in ChemDraw version 12.0, PerkinElmer Infromatics [13].

RESULTS

In this study SmPCs of 21 registered products were analyzed. Three medicines (tablet formulations) were excluded from the study because sodium content was not stated. Authors divided data in three tables, relative to dosage form: effervescent tablets (Table 1.), effervescent granules (Table 2.) and effervescent powders (Table 3.). Average sodium content was calculated for analyzed medicines in three different dosage forms and is 293.20 mg in effervescent tablets, 143.89 mg in effervescent granules and 178.00 mg in effervescent powders.

There are 5 formulations in which exposure to sodium through consumption of maximum daily doses exceeds AI and RDI both, all of which are effervescent tablet formulations: T3 (acetylsalycic acid 500 mg) , T2 (acetysalicylic acid 500 mg and ascorbic acid 250 mg), T4 (acetysalicylic acid 400 mg and ascorbic acid 240 mg), T6 (paracetamol 500 mg) and T7 (paracetamol 330 mg and ascorbic acid 200 mg). The highest exposure to sodium was found in formulation T3, effervescent tablets containing acetylsalycic acid (500 mg) as an active pharmaceutical ingredient (Table 1.): 217.20 % for people aged 18 to 50 years; 250.62 % for people aged 51 to 70 years; 271.50 % for people aged 70 and older.

In Figure 1. exposure to sodium through consumption of maximum daily doses as percentage of the AI for two age groups is shown: people aged from 51 to 70 years and people over 70 years of age, as these age groups are particularly prone to hypertension.

In Table 4. are listed sodium containing excipients. Every analyzed formulation contains sodium hydrogen carbonate. Sodium carbonate, anhydrous and saccharine sodium are the other two most commonly found excipients, in 61.90% and 52.38% of analyzed formulations respectively.

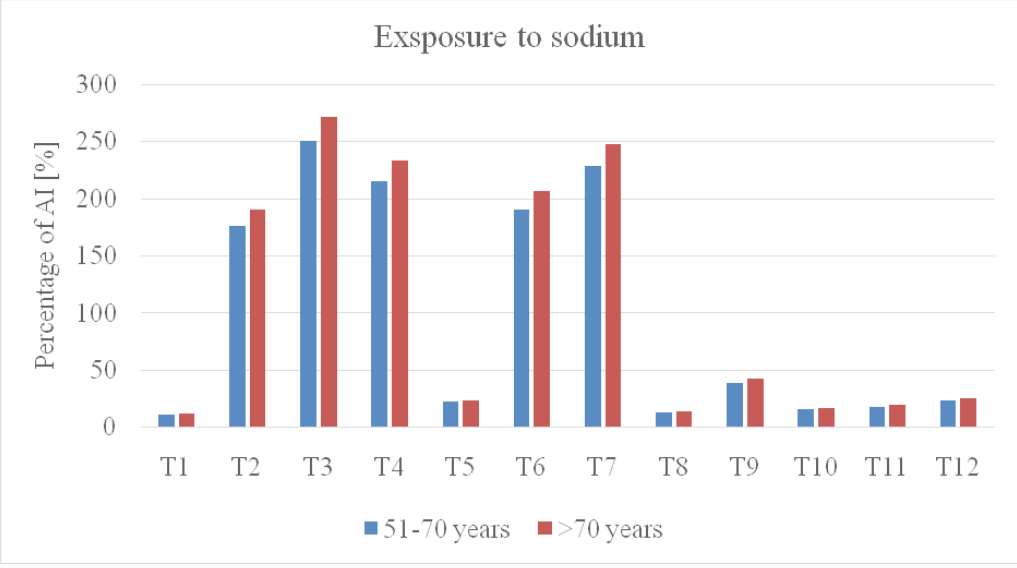


Figure 1. Percentage of the AI of sodium through consumption of maximum daily doses from effervescent tablet formulations (T1-T12, Table 1.) for two age groups

Table 1. Effervescent tablet formulations available in Serbia

Formulation	Active pharmaceutical ingredients	Na content per dose unit [mg]	Maximum daily dose [in dose units]	Na content in maximum daily dose [mg]	Exposure to sodium [% of RDI]	Exposure to sodium [% of AI]
T1	acetylcysteine 600 mg	139.00	Older than 14 years: 1	Older than 14 years: 139.00	6.95%	14-50 years: 9.27% 51-70 years: 10.69% >70 years: 11.58%
T2	acetysalicylic acid 500 mg; ascorbic acid 250 mg	381.04	Children older than 16 years: 3 Adults: 6	Children older than 16 years: 1143.12 Adults: 2286.24	57.16% 114.31%	16-18 years: 76.21% 18-50 years: 152.42% 51-70 years: 175.86% >70 years: 190.52%
T3	acetysalicylic acid 500 mg	543.00	Older than 16 years: 6	Older than 16 years: 3258.00	162.90%	16-50 years: 217.20% 51-70 years: 250.62% >70 years: 271.50%
T4	acetysalicylic acid 400 mg; ascorbic acid 240 mg	466.40	Older than 16 years: 6	Older than 16 years: 2798.40	139.92%	16-50 years: 186.56% 51-70 years: 215.26% >70 years: 233.20%
T5	ascorbic acid 1000 mg; calcium carbonate 327 mg; calcium lactate gluconate 1000 mg	280.00	Adults and school-aged children: 1	Adults and school-aged children: 280.00	14.00%	6-8 years: 23.33% 9-50 years: 18.67% 51-70 years: 21.54% >70 years: 23.33%
T6	paracetamol 500 mg	412.40	Older than 12 years: 6	Older than 12 years: 2474.40	123.62%	12-50 years: 164.96% 51-70 years: 190.34% >70 years: 206.20%
T7	paracetamol 330 mg; ascorbic acid 200 mg	330.00	8-10 years: 5 10-12 years: 6 12-15 years: 7 Adults (older than 15 years): 9	8-10 years: 1650.00 10-12 years: 1980.00 12-15 years: 2310.00 Adults (older than 15 years): 2970.00	148.50%	8 years: 137.50% 9-10 years: 110.00% 10-12 years: 132.00% 12-15 years: 154.00% 15-50 years: 198.00% 51-70 years: 228.46% >70 years: 247.50%
T8	acetylcysteine 600 mg	156.90	Adults: 1	Adults: 156.90	7.85%	18-50 years: 10.46% 51-70 years: 12.07% >70 years: 13.08%
T9	acetylcysteine 200 mg	166.60	Adults: 3 Children aged 6 to 12 years: 2	Adults: 499.80 Children aged 6 to 12 years: 333.20	24.99%	6-8 years: 27.77% 9-12years: 22.21% 12-50 years: 33.32% 51-70 years: 38.45% >70 years: 41.65%
T10	acetylcysteine 600 mg	194.00	Adults: 1	Adults: 194.00	9.7%	18-50 years: 12.93% 51-70 years: 14.92% >70 years: 16.17%
T11	*Hedera helix L.*, dry leaf extract 65 mg	151.33	Adolescents (children aged 12 and older), adults and elderly: 1½ Children aged 6 to 11 years: 1	Adolescents (children aged 12 and older), adults and elderly: 227.00 Children aged 6 to 11 years: 151.33	11.35%	6-8 years: 12.61% 9-11 years: 10.09% 12-50 years: 15.13% 51-70 years: 17.46% >70 years: 18.92%
T12	ascorbic acid 1000 mg	297.74	1	297.74	14.89%	1-3 years: 29.77% 4-8 years: 24.81% 9-50 years: 19.85% 51-70 years: 22.90% >70 years: 24.81%

Table 2. Effervescent granule formulations available in Serbia

Formulation	Active pharmaceutical ingredients	Na content per dose unit [mg]	Maximum daily dose [in dose units]	Na content in maximum daily dose [mg]	Exposure to sodium [% of RDI]	Exposure to sodium [% of AI]
G1	ibuprofen 400 mg	100.00	Adults and adolescents over 12 years of age (body weight more than 40 kg): 3	Adults and adolescents over 12 years of age (body weight more than 40 kg): 300.00	15.00%	12-50 years: 20.00% 51-70 years: 23.08% >70 years: 25.00%
G2	ibuprofen 600 mg	197.00	Adults and adolescents over 12 years of age (body weight more than 40 kg): 4	Adults and adolescents over 12 years of age (body weight more than 40 kg): 788.00	39.40%	12-50 years: 52.53% 51-70 years: 60.61% >70 years: 65.67%
G3	paracetamol 500 mg; phenylephrine 10 mg; chlorphenamine 4 mg	144.00	Adults (older than 12): 4	Adults (older than 12): 576.00	28.80%	12-50 years: 38.40% 51-70 years: 44.31% >70 years: 48.00%
G4	paracetamol 500 mg; pseudoephedrine 60 mg; chlorphenamine 4 mg	134.57	Adults: 4	Adults: 538.28	26.91%	18-50 years: 35.89% 51-70 years: 41.41% >70 years: 44.86%

Table 3. Effervescent powder formulations available in Serbia

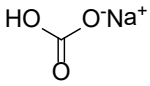
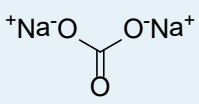
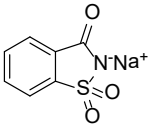
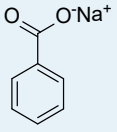
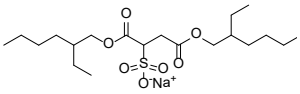
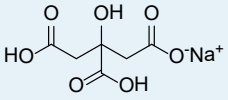
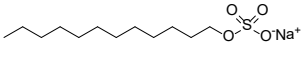
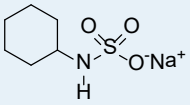
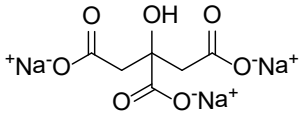
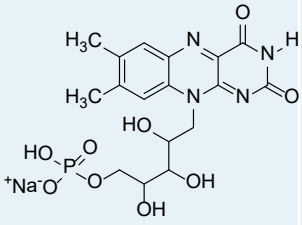
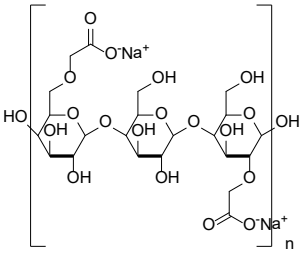
Formulation	Active pharmaceutical ingredients	Na content per dose unit [mg]	Maximum daily dose [in dose units]	Na content in maximum daily dose [mg]	Exposure to sodium [% of RDI]	Exposure to sodium [% of AI]
P1	acetylsalicylic acid 500 mg; ascorbic acid 500 mg; calcium lactate gluconate 1550 mg	178.00	Over 16 years of age: 4	Over 16 years of age: 712.00	35.60%	16-50 years: 47,47% 51-70 years: 54,76% >70 years: 59,33%
P2	acetylsalicylic acid 500 mg; ascorbic acid 500 mg; calcium lactate gluconate 1550 mg	178.00	Over 16 years of age: 4	Over 16 years of age: 712.00	35.60%	16-50 years: 47,47% 51-70 years: 54,76% >70 years: 59,33%

DISCUSSION

The main source of sodium intake is bread, cheese and processed food, which are estimated to contribute up to 75% of daily salt intake [14, 15]. Another 20% percent are considered be salt added by the consumer, which leaves 5% coming from water and medicines [14]. Although only a small percent of sodium comes from medicines consumption, it should not be overlooked. This source can easily be lowered by switching patients from high-sodium containing medicines to other formulations with low sodium content.

A study in France has found that a proportion of patients that can't be neglected was exposed to more than 20% of the WHO's dietary sodium intake recommendations [9]. In our study, 11 of 21 analyzed medicines could overpass this threshold of 20% of daily

Table 4. Sodium containing excipients in analyzed medicines

Excipient	Chemical structure	Formulations which contain the excipient	Percentage of analyzed formulations which contain the excipient [%]	Functional Category
Sodium Hydrogen Carbonate		All	100	disintegrant, effervescent agent, alkalizing agent
Sodium Carbonate, Anhydrous		T1, T2, T3, T4, T5, T6, T7, T9, T11,T14,T15, G1, G2	61.9	disintegrant, effervescent agent, alkalizing agent
Saccharine Sodium		T1, T5, T6, T7, T9, T12, T13, T14, T15, G1, G2	52.38	sweetening agent
Sodium Benzoate		T7, T8, T9, T11, T15, G3, G4	33.33	lubricant
Docusate Sodium		T2, T7, T8, T9, T11	23.81	wetting agent
Sodium Dihydrogen Citrate		T2, T3, T4, T6	19.05	solubility enhancer, disintegrant, sequestering agent, alkalizing agent
Sodium Laurilsulfate		P1, P2, G1, G2	19.05	lubricant, wetting agent
Sodium Cyclamate		T1, T2, T14	14.29	sweetening agent
Sodium Citrate		T1, T2, T14	14.29	solubility enhancer, disintegrant, sequestering agent, alkalizing agent
Riboflavin Sodium Phosphate		T11	4.76	coloring agent
Croscarmellose Sodium		G2	4.76	disintegrant

sodium intake through consumption of maximum daily dose: 6 tablet formulations (T2, T3, T4, T6, T7, T9 in Table 1.), 3 effervescent granules (G2, G3, G4 in Table 2.) and 2 powder formulations (P1, P2 in Table 3.).

Perrin et al. (2018) have concluded that daily sodium intake through consumption of high-sodium containing medicines (such as effervescents) higher than 1500 mg, long-term exposure to these medicines, as well as presence of comorbidities (especially hypertension and diabetes mellitus) increase the risk of cardiovascular complications [15]. By this criteria, effervescent granules (Table 2.) and powders (Table 3.) registered in Serbia do not contain a worrying amount of sodium. However, five effervescent tablet formulations (T2, T3, T4, T6, T7) were found to have more than 1500 mg of sodium in maximum daily dose. Formulations T3 (acetylsalicylic acid) and T6 (paracetamol) contain analgesic as API. Effervescent formulations with paracetamol (3g/day) can be used as treatment for some chronic conditions like osteoarthritis [14]. Formulations T2, T4 and T7 contain ascorbic acid combined with either acetylsalicylic acid or paracetamol as API and are usually indicated for treatment of common cold, flu symptoms and acute pain. These formulations are most commonly used only for short periods of time. However, in patients who use effervescents long-term for chronic conditions, additional consumption of effervescent formulations for acute medical episode (e.g., sciatica, common cold, flu) lead to sudden increase of sodium and enhance the risk of cardiovascular complications [9, 16].

Patients' impression that effervescent dosage forms act faster could lead to their preference over tablets and capsules, especially with analgesic as API [9]. In Serbia, ibuprofen, paracetamol and acetysalicylic acid are available both as effervescent tablets and/or granules and oral tablets. It is also important to mention that all of the analyzed medicines are available as over-the-counter medicine, apart from effervescent granule formulation G2 (ibuprofen, 600 mg) (Table 2.), which is prescription-only [12]. This may lead to the fact that general practitioners are often unaware that patients use over-the-counter effervescents for self-medication. Furthermore, NSAIDs are known to have potential to worsen hypertension in some patients by salt and fluid retention [17]. Therefore, community pharmacist should be trained to advise patients for which benefits of effervescent dosage forms (e.g., faster therapeutic action) do not outweigh risk of cardiovascular complications, to take a nonhigh sodium-containing formulation instead.

There is a controversy regarding anions in sodium salts. There are studies which have confirmed effect of sodium chloride on blood pressure, but do not associate sodium bicarbonate unambiguously [18, 19]. Sodium bicarbonate is excipient found in each analyzed formulation (Table 4.), as it is the main compound of effervescent dosage forms. One study has shown that both sodium bicarbonate and sodium chloride can be associated with elevation of blood pressure in salt-sensitive patients. Even though sodium bicarbonate showed half of the hypertensive effect that of sodium chloride, effect on blood pressure of neither salt can't be neglected [20]. Unfortunately, there is no data about quantity of each sodium containing excipient in analyzed medicines, only the total amount of sodium. Further studies are needed to investigate which compounds containing sodium are the ones having the significant effect on blood pressure.

Knowing the complete quantity of contents and role of each ingredient gives opportunity for compounding of new ex tempore medicines, switching potentially harmful excipients with safe ones from the same functional category.

It is important to mention that this study has included only effervescent medicines registered in Serbia. Dietary supplements, however, where not included. Due to their ease of access and belief among patients that dietary supplements are very safe, effervescent vitamin and mineral supplements are widely used. Additionally, dietary supplements can be used for longer periods of time.

CONCLUSION

Hypertension as the main factor for developing CVDs represents a significant issue of today society. It is known that sodium has negative effect on hypertension and therefore regulatory bodies give recommendations for limited sodium intake. On the other hand, sodium-contained compounds are common ingredients in pharmaceutical industry and can be found in many approved medicines.

In effervescent dosage forms avail-

able on Serbian market, level of sodium to which patient can be exposed to through consumption of these medicines may be even more than two times higher than AI. Major cause for concern is for patients who use effervescents long-term. This data should be considered during prescribing and dispensing this category of medicines as well as during analyzing pharmacovigilance.

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CONFLICT OF INTEREST

All authors declare no conflict of interest.

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Unos natrijuma putem lekova - Upozorenje pri lečenju kardiovaskularnih bolesti

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KRATAK SADRŽAJ

Uvod: Hipertenzija je stanje koje predstavlja jedan od glavnih faktora rizika za razvoj kardiovaskularnih bolesti. Visok unos natrijuma doprinosi pojavi hipertenzije, povećavajući volumen ekstracelularne tečnosti. Stoga Svetska Zdravstvena Organizacija i druga udruženja uključena u istraživanje hipertenzije savetuju smanjenje unosa natrijuma. Šumeći dozirani oblici obično sadrže veću količinu natrijuma, što može dovesti do pomenutih zdravstvenih problema.
Cilj: Cilj ove studije bila je procena nivoa natrijuma u šumećim doziranim oblicima dostupnim na tržištu lekova u Srbiji.
Metode: Podaci o nivou natrijuma i pomoćnim sastojcima dobijeni su iz Sažetka karakteristika leka sa veb stranice Agencije za lekove i medicinska sredstva Srbije (ALIMS). Primećene su maksimalne dnevne doze koje je preporučio proizvođač i odobrila ALIMS. Izloženost natrijumu kroz konzumiranje maksimalnih dnevnih doza izračunata je kao procenat adekvatnog dnevnog unosa koji daje *Food and Nutrition Board, Institute of Medicine, National Academies*, a takođe i kao procenat preporučenog dnevnog unosa natrijuma, koji daje Svetska zdravstvena organizacija.
Rezultati: Pronađeno je pet formulacija za koje je izloženost natrijumu konzumiranjem maksimalnih dnevnih doza viših od 100% adekvatnog dnevnog unosa koji iznosi 2 g, a sve su šumeće formulacije tableta. Najveća izloženost natrijumu pronađena je u šumećim tabletama koje sadrže acetilsalicinsku kiselinu (500 mg) kao aktivni farmaceutski sastojak: 250,62% za osobe starije od 51 do 70 godina; 271,50% za osobe starije od 70 godina.
Zaključak: U šumećim doziranim oblicima dostupnim na tržištu u Srbiji nivo natrijuma može biti mnogo veći od adekvatnog dnevnog unosa (čak i do 271,50% adekvatnog dnevnog unosa) kada se konzumiraju maksimalne dnevne doze. Glavni razlog za zabrinutost je kod pacijenata koji koriste šumeće lekove za hroničnu terapiju. Ove podatke treba uzeti u obzir tokom propisivanja i izdavanja ove kategorije lekova, kao i tokom analize farmakovigilance.

Ključne reči: pomoćne supstance, sadržaj natrijuma, hipertenzija, vaskularna terapija

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