

## THE INFLUENCE OF HYPOTENSIVE DRUGS ON THE TASTE SENSITIVITY IN PATIENTS WITH PRIMARY HYPERTENSION

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**Abstract:** Numerous hypotensive drugs result in decreasing the taste sensitivity or total loss of taste perception. The aim of this study was to evaluate the influence of selected groups of hypotensive drugs used in combined treatment of the taste sensitivity in patients suffering from primary arterial hypertension. The study was conducted in a group of 84 patients aged 30-60, including 43 women and 41 men. The patients were divided into four groups depending on the applied combined treatment including the following treatment regimes: diuretic +  $\beta$ -blocker, diuretic +  $\beta$ -blocker + ACE-I, ACE-I + diuretic, ACE-I + diuretic + calcium channel blocker. The study involved also control group of 20 healthy people (without medications) aged 30-60, including 10 women and 10 men. Taste sensitivity was evaluated by two methods: chemosensory and electrogustometric. Chemosensory method was used to assess the sensitivity to salt and sweet tastes with the use of increasing concentrations of saccharose water solutions (0.012-0.041 mmol/L) and water solutions of sodium chloride (0.008-0.068 mmol/L). Electrogustometric thresholds of taste sensitivity were established with electrogustometer. The minimal intensity of the current, which stimulates nerve endings of the taste stimuli-transmitting nerves was determined in two areas of the tongue: at the apex and at the sides. By two different methods of evaluation it was shown that the analyzed groups of hypotensive drugs affect the taste sensitivity of the patients. It was observed that healthy people had higher taste sensitivity than patients. Introducing ACE-I into combined therapy significantly reduced the electrogustometric sensitivity in patients.

**Keywords:** drugs, taste, hypertension, electrogustometry, chemosensory thresholds

**Abbreviations:** ACE-I – angiotensin converting enzyme inhibitors, HT – hypertension

Disorders of senses, which result in the impairment of sensory functions, occur in the course of many diseases (1–3). In metabolic diseases, including arterial hypertension, the sense of taste deserves particular attention.

Decreasing the sensitivity to salty taste in patients suffering from HT (hypertension) was indicated by the research carried out by Michikawa et al. (4) and Isezuo et al. (5). According to Doty et al. (6, 7) the physiological reasons of dysgeusia and hypogeusia have not been entirely investigated.

It is assumed that some diseases impair chemoperception in the following way: stopping or slowing down the regeneration of receptor cells, hindering or blocking the conduction of signals

stimulating the receptors to the cerebral cortex, disturbing the functioning of the central nervous system – affecting particularly the cerebral cortex centers responsible for taste and odor identification based on the smell and taste memory. Changes in taste sensitivity can result from functional disorders of sensory cells in nerves (nerves: VII, IX, X) (8, 9). It is also assumed that this type of dysfunction can be related to deficiencies of some vitamins and mineral compounds in the organism (vitamin B<sub>12</sub>, zinc, iron) (7, 8).

In the case of patients suffering from HT, Ukoh et al. (10) and Baryłko-Pikielna et al. (11) claim that higher threshold of sensitivity to salty taste in patients can be related to disorders in sodium metabo-

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olism. It appears that the reason behind the decreased taste perception in HT patients can be both primary and secondary. The idea of primary causes of taste disorders in HT is supported by the research results obtained by Zinner et al. (12). It was concluded that the genetically determined hypertension was related to increased preference for salty taste. This idea is also confirmed by observation carried out among young people, which also showed a negative correlation between the value of blood systolic pressure and their sensitivity to salty taste (13). It seems that the decreased taste sensitivity in patients suffering from HT can also result from this disease (14, 15). It was partially confirmed by animal experimentation, which showed that increased levels of aldosterone and angiotensin II can result in blocking the sensitivity to salty taste (16). Drugs used by patients can also be included in the secondary causes of decreased gustatory perception (17–19). It was showed that some groups of hypotensive drugs decrease the taste sensitivity in patients, who use them. Decreasing the sensory sensitivity was observed in 70% of the cases of using ACE inhibitors in monotherapies and in 65% cases of combined therapies (20). Golik et al. (21) observed that the patients treated with ACE inhibitors (captopril and enalapril) suffer from zinc deficiency. It is suspected by the authors that it could be the cause of gustatory disorders in this group of patients.

Taste perception disorders affect developing certain eating habits, which influence the chosen food products (22). Unbalanced nutrition including, among others, eating excessive amounts of monosaccharides and salt can contribute to decreasing the treatment effectiveness and disease development.

In this study we attempted to evaluate the influence of chosen groups of hypotensive drugs used in combined therapy on taste sensitivity in patients suffering from primary arterial hypertension.

## EXPERIMENTAL

The study protocol was approved by Bioethics Commission at Poznań University of Medical Sciences – Bioethics Commission Approval No.: 346/02.

### Subjects

The study group of 84 subjects aged 30 to 60 years with primary hypertension – 1<sup>st</sup> or 2<sup>nd</sup> stage as defined by the criteria of *Joint National Committee VII* – included 43 females (mean age: 51.0 ± 8.1 years) and 41 males (mean age: 49.2 ± 7.9 years). The subjects were receiving pharmacological treatment in the Clinic of Internal Diseases, Metabolic Disorders and Arterial Hypertension at Poznan University of Medical Sciences, Poland.

All of the subjects received combined anti-hypertensive treatment of two or three drugs for 5–10 years, i.e., diuretic +  $\beta$ -blocker (23% of patients), ACE-I (angiotensin converting enzyme inhibitors) + diuretic (29% of patients), ACE-I + diuretic + calcium channel blocker (24% of patients) and ACE-I + diuretic +  $\beta$ -blocker (24% of patients) (Table 1). Patients received different combinations of antihypertensive drugs. In a group of diuretics were: indapamide, hydrochlorothiazide, furosemide, clopamide, ACE-I group included: enalapril, perindopril, lisinopril, ramipril, trandolapril, in a group of  $\beta$ -blockers were used: bisoprolol, propranolol, metoprolol, nadolol, and in a group of calcium channel blocker were: amlodipine, nitrendipine and verapamil. In any group of patients there were no significant advantage of any of the antihypertensive drugs.

None of the patients reported problems with taste or smell functions. In study group there were 16 smokers and 5 patients wore dentures. Patients with comorbid disorders, such as cardiac ischemic disease, history of myocardial infarction, renal

Table 1. Percentage of patients using selected groups of hypotensive drugs.

Type of therapy	Group of drugs	% of subjects (n = 84)
Combined therapy	Diuretics + $\beta$ -blockers (I)	23
	ACE-I + Diuretics (II)	29
	ACE-I+ Diuretics + Calcium channel antagonist (III)	24
	ACE-I + Diuretics + $\beta$ -blockers (IV)	24

ACE-I – angiotensin converting enzyme inhibitors. (I–IV) – number of group.

Table 2. The concentrations of standard solutions of saccharose ( $C_{12}H_{22}O_{11}$ ) and sodium chloride (NaCl).

Sacharose [mol/L]	Sodium chloride [mol/L]
0.00 (blank)	0.00 (blank)
0.012	0.008
0.023	0.026
0.029	0.041
0.041	0.068

insufficiency, diabetes mellitus, gout or hyperlipidemia were excluded from the study.

The control group involved 20 healthy people aged 30–60 years, including 10 women and 10 men, which were not receiving medications. The control group did not differ statistically in age from the hypertensive groups.

All subjects were informed about the aim of the study, procedures and measurement methods and all expressed their consent in writing to enroll in the study.

### Measurement of taste sensitivity

#### *Chemosensory method*

Individual thresholds of taste sensitivity to sweet and salty tastes were determined in this study. Individual threshold values for recognizing tastes were established by determining the lowest concentration of the stimulus, which resulted in the transfer from no reaction to perceptible gustatory sensation. The quality of the sensation was assessed simultaneously. Each subject was given a number of water solutions with gradually increasing concentrations of the standardized substances. It allowed for creating a set of stimuli increasing in intensity. In order to determine the individual thresholds of sensitivity to sweet and salty taste, four sucrose solutions and four sodium chloride solutions were prepared. The concentrations are presented in Table 2. One blank solution (distilled water) was presented during chemosensory testing to minimize biases. The solutions were prepared with the above mentioned chemical substances and taste-neutral, freshly distilled water. The solutions were prepared in identical, coded plastic 100 mL bottles made of polyethylene (admitted for direct contact with food). Fifteen mL of each solution at room temperature was given to the subjects for organoleptic assessment. Between testing samples of different tastes, the subjects

rinsed their mouth with distilled water. The analysis started from the evaluation of sucrose solutions with 30 s breaks between consecutive samples. Then, after 15 min of break, the subjects were given the sodium chloride solutions. The subjects were holding the samples in their mouth for 5–6 s. Afterwards, the samples were spat out into plastic containers. Patients tasted each solution only once. Patients had to report whether they could detect taste and recognize it. The testers were blind to the subject group. Patients were asked to refrain from food and drink for two hours before testing. The organoleptic analysis was carried out under identical conditions for all subjects. It took place in a 10 m<sup>2</sup> room without windows, at the temperature of 20°C. The room had white walls and the light intensity was 100 W. The experiment was conducted between 10 a.m. and 12 p.m.

#### *Electrogustometric method*

The evaluation of taste perception by electrogustometric method was carried out by determining the minimal values of the current intensity, which stimulated the nerve endings conducting the taste stimuli in the mouth cavity. The value of the intensity of current, expressed in microamperes [mA], constitutes the electrogustometric threshold of taste perception. The threshold was determined by the measurements performed by electrogustometer device. The electrogustometer was designed and manufactured at Poznan University of Medical Sciences. The device was powered by batteries and it was composed of a measurement device, microamperemeter, a set of big resistors and a knob for adjusting the range of current intensity. The range of intensity was adjustable (1–1000 mA). Two electrodes were parts of the equipment of the device. The electrode put on the wrist was an anode, while the other one, periodically touching certain areas of the tongue, was a cathode. Prior to placing the anode on the wrist, a drop of physiological solution was applied to the area of contact with the electrode. The cathode was disinfected in ethanol and rinsed in distilled water after each use.

The following areas of the tongue were included in the taste sensitivity study: left and right margin of the tongue, 1.5 cm from the back of the tongue and the apex of the tongue.

The measurement was initiated by touching the tongue with an electrode without voltage (blank), and then gradually increasing its intensity by 1 mA after turning the current on. This was done until the subject reacted to the stimulus by sensing light stinging or metallic taste. The intensity of current,

which triggered one of these reactions, was assumed to be the stimulating threshold for the nerve endings. This procedure was performed once in each subjects.

Repeatability of chemosensory and electrogustometric methods was conducted and confirmed in a group of 20 volunteers aged 20–25 years.

### Statistical analysis

Statistica 6.0 software (StatSoft) was used for statistical analysis of the results. The key descriptive parameters, i.e., arithmetic mean, standard deviation and percentage distribution, were calculated. Kruskal-Wallis test and  $\chi^2$  test were used to establish significance of group differences at the significance level of  $\alpha = 0.05$ .

## RESULTS

The relation between the applied group of drugs and the taste perception was assessed in the patients. In order to accomplish this, the sensory sensitivity of the patients treated with four groups of drugs most commonly used in the Clinic of Internal Diseases, Metabolic Disorders and Arterial Hypertension of

Poznan University of Medical Sciences was compared. The following groups of drugs were used: combination of diuretic with  $\beta$ -blocker (group I), ACE-I with diuretic (group II), ACE-I with diuretic and calcium channel blocker (group III) or ACE-I with diuretic and  $\beta$ -blocker (group IV).

The obtained results indicated that the control group had the highest level of salty and sweet taste perception (Table 3). It was observed that the sweet taste sensitivity was decreased in patients treated with a combination of diuretic and  $\beta$ -blocker comparable to the control group (Table 3). None of the subjects in this group was able to sense the sweet taste in the lowest concentration of the saccharose solution. The biggest number of patients (50%), who were characterized by the highest sensitivity of sweet taste, were found in the group treated with the combination of ACE-I, diuretic and  $\beta$ -blocker. Subjects in this group (IV) had comparable thresholds of sweet taste to healthy people. At the same time the patients treated with the combination of ACE-I with diuretic and calcium channel blocker were observed to have the lowest level of salty taste perception (Table 3). In the remaining groups it was also observed that a high percentage of patients

Table 3. Percentage of patients according to chemosensory taste thresholds.

Groups	Taste thresholds [mol/L]							
	Sweet				Salty			
	0.012	0.023	0.029	0.041	0.008	0.026	0.041	0.068
Control <sup>b</sup>	55	26	19	0	23	57	20	0
Diuretics + $\beta$ -blockers (I) <sup>a</sup>	0	38	38	24	12	38	25	25
ACE-I + Diuretics (II) <sup>a,b</sup>	35	15	25	25	10	45	40	5
ACE-I + Diuretics + Calcium channel blockers (III) <sup>a,b</sup>	36	6	29	29	0	14	36	50
ACE-I + Diuretics + $\beta$ -blockers (IV) <sup>b</sup>	50	18	19	13	6	31	38	25

$\chi^2$  test; <sup>a,b</sup> differences between groups for sensitivity of sweet taste;  $p < 0.05$

Table 4. Electrogustometry taste thresholds [ $\mu$ A].

Groups	Taste thresholds [mean $\pm$ SD]	
	Part of the tongue	
	Apex	Sides
Control	15.2 $\pm$ 3.0 <sup>a</sup>	26.2 $\pm$ 4.2 <sup>a</sup>
Diuretics + $\beta$ -blockers (I)	27.9 $\pm$ 4.2 <sup>a,b</sup>	30.0 $\pm$ 4.8 <sup>a,b</sup>
ACE-I + Diuretics (II)	32.0 $\pm$ 5.7 <sup>a,b</sup>	43.0 $\pm$ 4.2 <sup>b,c</sup>
ACE-I + Diuretics + Calcium channel blockers (III)	59.0 $\pm$ 11.3 <sup>c</sup>	64.0 $\pm$ 12.4 <sup>c</sup>
ACE-I + Diuretics + $\beta$ -blockers (IV)	32.0 $\pm$ 6.3 <sup>a,b</sup>	55.5 $\pm$ 14.2 <sup>c</sup>

Kruskal-Wallis test; <sup>a,b,c</sup> difference between groups for sensitivity of part of the tongue;  $p < 0.05$

could recognize the salty taste in relatively high concentrations of sodium chloride. Statistically significant differences in the sweet taste sensitivity were observed between the groups I and IV and between control group and group I.

In Table 4 it was shown that control group had markedly lower electrogustometric thresholds (higher taste perception) at the side of the tongue than patients treated with ACE-inhibitors. It was also observed that the subjects whose pharmacotherapy included a combination of diuretics and  $\beta$ -blockers were found to have comparable electrogustometric thresholds of taste sensitivity to healthy people. Patients in III group (ACE-I + diuretics + calcium channel blockers) had the lowest taste perception at the apex of the tongue compared to other groups. Patients, who were advised to use a combination of ACE-I with a diuretic and a  $\beta$ -blocker (IV) or with calcium channel blockers (III) in their therapy had significantly higher electrogustometric threshold of taste sensitivity (measured at the side of the tongue) than the patients using diuretic combined with  $\beta$ -blocker but without ACE inhibitor (I). It was observed that the value of electrogustometric threshold measured at the sides of the tongue in patients treated with ACE-I, diuretic and calcium channel blocker is higher (but not significantly) compared to the remaining groups of drugs (Table 4).

The conducted research did not reveal any significant influence of additional factors such as sex, age, smoking tobacco or wearing dentures on the taste sensitivity of the subjects (logistic regression model).

## DISCUSSION AND CONCLUSION

Decreasing the taste sensitivity or total loss of taste perception (ageusia) is an adverse effect of many drugs used in the cardiovascular diseases (23). Such drugs include among others: angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers. The extent to which hypotensive drugs used in different combinations in combined therapies affect the taste perception was not described in any published research available to us.

In this study, the taste sensitivity was evaluated by chemosensory and electrogustometric gustatory methods in patients with primary arterial hypertension using combined therapy with different regimens of hypotensive treatment. It was shown that the applied combinations of hypotensive drugs resulted in decreasing the taste perception in patients to a different extent.

The results of this study and the studies of other researchers do not indicate any significant correlation between the results obtained by the electric and chemical stimulation methods (24, 25). According to Stevens et al. (25), the differences result from a different mechanism of action of those two methods. In our study one can observe yet another tendency. In the case of salty taste in patients treated with a diuretic with ACE-I and calcium channel blocker, the highest thresholds of taste sensitivity were shown both by the electrogustometric and chemosensory methods.

It is known that different parts of the tongue (apex, root, sides) are characterized by different sensitivity to electric stimuli. In this study the taste sensitivity was evaluated by electrogustometric method on the apex of the tongue and on the sides of the tongue. Then, the measured values obtained on the left and on the right side of the tongue, were averaged. McMahon et al. (26) postulates that the taste sensitivity of the left and the right sides of the tongue is identical in most people. However, there are single cases of patients, in whom a significant difference in taste sensitivity between the left and the right side of the tongue was observed. Such difference was not observed in any of the subjects in the course of our examination.

In this study, higher electrogustometric thresholds were observed in patients using ACE-I among other drugs in combined therapy. This may suggest zinc deficiency in their organisms. The findings of other authors, who also observed decreased levels of zinc in patients using ACE-I, confirm these results (27). Low level of zinc in the organism can result in hypoguesia (28, 29). The recent publication of Takaoka et al. (30) confirms that zinc supplementation in patients treated with ACE-I, improved their taste sensitivity. Such relation was not observed in this study. It is possible that extending the study by including the investigation of relations between different drugs and the blood concentration of zinc in blood and hair of the patients in the study, could result in explaining the difference in chemosensory and electrogustometric thresholds in patients using different groups of drugs, indicated in the above mentioned study.

Patients using the angiotensin II receptor blockers were not included in this study, however, the results obtained by other researchers indicate that this group of drugs results in decreasing the taste sensitivity or ageusia. Tsuruoka et al. (31) compared the influence that losartan (angiotensin II receptor blocker) and perindopril (angiotensin converting enzyme inhibitor) exert on the sense of taste.



In the mentioned study, the analyzed drugs were given to healthy volunteers for 14 days. It was concluded that losartan and perindopril result in decreasing both the chemosensory sensitivity and the electrogustometric sensitivity of the four basic tastes. However, the mentioned authors did not observe any relation between the used drugs and the levels of zinc in the serum and in the saliva of the volunteers, who enrolled in the study. Other clinical observations also indicate that using losartan results in impairing the sense of taste and in single cases it results in a total loss of taste perception (32). The mechanism of action of losartan is not known. It does not show any metal-chelating properties (for example zinc) similar to ACE-I.

In other studies it was shown that ACE inhibitors decrease the activity of sympathetic nervous system, while calcium channel blockers increase it (33). It was observed in this study that the significant differences between electrogustometric thresholds in patients using drugs with no ACE inhibitor (diuretic + blocker) and the same drugs with ACE inhibitor (Table 4) can explain the relation between ACE-I and the activity of nerve junctions.

Regardless of the negative impact of ACE-I on the taste perception, it is assumed that this group of drugs is better tolerated and relatively fewer side-effects are observed than in the case of others hypotensive drugs (34). Given the negative influence of the used hypotensive drugs on decreasing the taste sensitivity in the patients using them, it would be advisable to search and introduce measures preventing these (presumably reversible) disorders.

Jackson et al. (35) observed regression of the taste dysfunction after using enalapril in patients previously treated with captopril. Mayet (36) observed increasing taste sensitivity in a man (previously suffering from ageusia) after putting away a long-term therapy with pegylated interferon  $\alpha$  and ribavirin.

According to Tirgan (37), fluorouracil and leucovorin result in taste perception disorders in patients suffering from colorectal carcinoma. Including dexamethasone in the therapy resulted in partial or total regression of the disorders. The study conducted by the mentioned author suggests that usage of certain substances can counteract the decrease in taste perception caused by drugs. In the case of hypotensive drugs, there are few published studies, which suggest a drug or another substance that could alleviate the symptoms of decreasing taste perception or its total loss. According to Takaoka et al. (30), zinc supplements can improve the taste sensitivity in the patients using ACE-I.

It should be mentioned that patients suffering from arterial hypertension, who did not undergo a hypotensive therapy, were observed to have decreased sensitivity to salty taste (38, 39). Lefrancq et al. (40) put forward a hypothesis that genetically determined sodium channel disorder is the reason of this problem. According to the mentioned authors, the dysfunction of sodium channels affects the incorrect sodium reabsorption in kidneys and it contributes to decreased perception of the salty taste in the anterior part of the tongue. In the light of this hypothesis it can be assumed that some of the hypotensive drugs are an additional factor decreasing the taste sensitivity through affecting the way sodium channels function.

Changes in taste perception are a common reason for discontinuing the drug therapy by patients suffering from arterial hypertension, which poses a serious threat to their lives (6). Henkin (1) noted that the therapy of taste perception disorders related to used drugs, should include the functioning of the receptors of senses and physiological factors affecting the correct functioning of the sense of taste, among others the level of zinc and magnesium.

In conclusion, it should be stated that the analyzed groups of hypotensive drugs affect the taste sensitivity of patients. It is most visible in patients treated with ACE-I combined with a diuretic and calcium channel blocker, which were proved to have the highest thresholds of electrogustometric perception. Not using ACE-I in a combined therapy with other analyzed drugs significantly decreases the threshold of taste sensitivity. However, this relation is not observed when the chemosensory method of taste perception evaluation is used. Based on the obtained results it can be concluded that it is necessary to continue the research on the way different hypotensive drugs and combined therapies affect the taste sensitivity in patients and design the methods of preventing or decreasing the adverse effects of these drugs.

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