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Prohypertensive Effects of Non-Steroidal Anti-Inflammatory Drugs are Mostly Due to Vasoconstriction

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A B S T R A C T

Non-steroidal anti-inflammatory drugs (NSAIDs) have prohypertensive effects and blunt the effects of many antihypertensives. The mechanism of this interaction is still not understood enough. The objective of this investigation was to determine the level of prohypertensive effects of two NSAIDs (ibuprofen, piroxicam) and paracetamol, co-prescribed with two antihypertensive drugs (lisinopril + hydrochlorothiazide, amlodipine), and to improve the understanding of this interaction. A prospective clinical trial, conducted in a Croatian family practice, included 110 already treated hypertensive patients, aged 56–85 years; 50 control patients and 60 patients who were also taking NSAIDs for osteoarthritis treatment. The antihypertensive regimens remained the same during this study, while NSAIDs and paracetamol were crossed-over in three monthly periods. Blood pressure, body weight, serum creatinine, potassium, sodium, diuresis and 24 h urinary sodium excretion were followed-up. In the lisinopril/hydrochlorothiazide subgroup, both ibuprofen and piroxicam elevated mean arterial pressure by 8.9–9.5% ($p<0.001$). Body weight increased significantly in the lisinopril/hydrochlorothiazide + piroxicam subgroup only, while creatinine, urinary output and electrolyte values did not change appreciably in any of the subgroups. NSAID's prohypertensive effects seem to be mostly due to vasoconstriction and, to a minor degree, to volume expansion, since no marked changes in body weight, urinary output, serum creatinine or serum/urinary electrolyte profile were observed.

Key words: *antihypertensive drugs, NSAIDs, interaction, vasoconstriction*

Introduction

Analgesic and anti-inflammatory properties of non-steroidal anti-inflammatory drugs (NSAIDs) derive from synthesis inhibition of several prostaglandins (arachidonic acid derivatives, eicosanoid group), mediated by cyclooxygenase (COX)[1]. Prostaglandins have various, often opposite, effects on different organs, e.g. a decrease in hydrochloric acid and pepsin secretion, an increase in the amount of mucus in the digestive system, a rise in glomerular filtration rate, a reduction in sodium, chloride and water reabsorption in the kidneys, a respiratory smooth muscle relaxation or an increase in afferent pain threshold[1]. Complex interactions between vasodilatory (e.g. PGE) and vasoconstrictive (e.g. TxA_2) prostanoids have been described, as well as interactions with other endothelial mediators like nitric oxide or endothelin[2].

There are different COX isoforms, the most prominent being constitutive

(COX-1) and inducible (COX-2) ones. COX-1 is permanently active in many tissues, regulating normal cellular activity (gastric mucosa, vascular endothelium, kidney tubules, platelets). COX-2 is constantly active in brain, kidneys and blood vessels; in the rest of the body, it is primarily induced by inflammation[1].

The NSAID's influence on arterial pressure has been widely investigated[3–20].

Prostaglandin synthesis inhibition can lead to significant interaction between NSAIDs and various antihypertensive drugs, especially if these agents are eicosanoid-dependent. It seems that ACE inhibitors, diuretics and

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β-blockers (and, to a lesser degree, angiotensin II receptor blockers) are more affected by this interaction, i.e. more susceptible to impaired control of elevated blood pressure (BP), whereas calcium channel blockers are more resistant[3,4]. The reasons why some antihypertensives behave differently in this respect are still unclear. For example, NSAIDs reduce natriuretic effect of diuretics (PGE dependent, especially PGE_2), and suppress diuretic-induced renin activation. ACE inhibitors' antihypertensive effect is probably weakened by NSAIDs' diminution in bradykinin secretion and subsequent release of vasodilatory and/or natriuretic compounds (e.g. nitric oxide). Possible mechanisms include different degrees of COX isoenzyme inhibition, different concentrations in critical biophase, or some side-effects (e.g. on angiotensin II or endothelin levels, or their receptor sensitivity)[3].

The objective of this study was to determine the prohypertensive effects of two NSAIDs (ibuprofen, piroxicam) and paracetamol when used in combination with lisinopril/hydrochlorothiazide or amlodipine, and to refine the understanding of this interaction (predominant influence on kidney function or on vascular resistance). Therefore, besides BP alterations this trial was designed to assess the changes in body weight, serum creatinine, sodium and potassium, diuresis, and 24 h urinary sodium excretion.

Materials and Methods

After signing informed consent, approved by the Split University School of Medicine Ethical Committee, 110 already treated hypertensive patients, aged above 55 years, were involved in this prospective clinical trial (ClinicalTrials.gov #NCT00631514)[3]. The initial results concerning NSAID effects on arterial blood pressure in a group of 88 patients have already been published[3]; here we present the data about body weight changes, serum creatinine, potassium and sodium values, urine output, sodium values in 24 h urine and mean arterial pressure for 110 examinees (final data), with some considerations of the mechanism of this interaction.

The control group consisted of 50 hypertensives treated for elevated blood pressure only, while the intervention group consisted of 60 hypertensives who were also taking NSAIDs for knee or hip osteoarthritis treatment. During this 3-month cross-over study, the interaction between antihypertensives (amlodipine or lisinopril/hydrochlorothiazide fixed combination) and analgesics (ibuprofen, paracetamol and piroxicam) was investigated.

The inclusion criteria for enrollment in the study were: either gender, age 55 or older, diastolic blood pressure of 90–100 mm Hg, absence of cardiac failure and serum creatinine below 150 μmol/l. The intervention group had additional inclusion criteria: concomitant knee or hip osteoarthritis requiring NSAIDs treatment. The exclusion criteria were: worsening of hypertension (diastolic blood pressure exceeding 110 mm Hg), myocardial infarction, necessity of additional antihypertensive treatment, failure to take the studied drugs for more than three days, considerable worsening of the joint condition after the NSAIDs exclusion. The examinees were not allowed to take other drugs that could alter renal function. Since all of them were already hypertensive, and previously instructed about dietary habits, no additional salt intake restrictions were recommended.

Following clinical work-up and discontinuation of NSAIDs for at least 3 days, the run-in period lasted 3–7 days. Wash-out was relatively short, since we could not

TABLE 1
BASELINE CHARACTERISTICS OF THE EXAMINEES

Study group	Control		Intervention				
Parameter	L/H	AM	L/H±IB	L/H±PX	AM±IB	AM±PX	p
Randomized (n)	25	25	15	15	15	15	
Male/female (n)	15/10	13/12	7/8	5/10	5/10	4/11	0.653
Age (years; $\overline{X}$±SD)	68.1±6.2	69.7±8.2	70.5±7.2	69.7±7.4	69.5±6.7	69.5±8.6	0.900
Weight (kg; $\overline{X}$±SD)	81.8±11.0	80.5±15.1	84.5±15.7	79.6±13.4	80.1±12.3	85.5±13.8	0.766
BMI (kg/m^2; $\overline{X}$±SD)	28.3±3.3	27.4±4.2	29.1±4.0	28.6±4.3	29.3±4.7	30.1±3.0	0.399
Systolic BP (mm Hg)	151.5±13.0	149.7±9.0	147.5±10.6	149.7±10.1	150.5±9.2	154.1±9.6	0.632
Diastolic BP (mm Hg)	88.7±6.4	86.8±5.7	85.7±6.8	86.7±5.7	84.0±8.8	86.9±8.6	0.469
Plasma creatinine (μmol/L)	91.8±18.2	97.6±23.3	91.5±25.3	92.3±24.1	86.9±18.4	78.0±5.9	0.342
Plasma sodium (mmol/L)	142.0±2.6	141.5±3.0	141.8±2.3	140.9±2.4	141.5±1.6	140.4±2.6	0.672
Urinary output (mL/24h)	1888.1±730.0	1696.0±548.9	1492.9±828.4	1737.5±406.5	2092.0±760.6	1331.3±407.9	0.093
Urinary sodium excretion (mmol/24h)	199.4±84.0	168.7±76.7	182.6±91.9	171.0±77.8	230.4±100.8	175.9±56.0	0.562

AM – amlodipine, BMI – body mass index, BP – blood pressure, IB – ibuprofen; L/H – lisinopril/hydrochlorothiazide, MAP – mean arterial pressure, PX – piroxicam, ±SD – Means ± standard deviations of the data

afford any longer period because of expected non-compliance (the patients would take some »pain-killers« anyway). The intervention group was randomized (sealed envelopes) in two subgroups; one taking ibuprofen 400–600 mg three times a day for 1 month, then paracetamol 1000 mg 2–3 times a day for another month, and finally taking the same ibuprofen dose for the 3rd month, while the other subgroup was taking piroxicam 10–20 mg once a day for 1 month, followed by paracetamol 1000 mg 2–3 times a day for another month, and resuming piroxicam in the 3rd month. All the examinees continued their antihypertensive medications throughout the study: lisinopril/hydrochlorothiazide 10/6.25–20/12.5 mg once a day or amlodipine 5–10 mg once a day. Individual drug dosage was titrated before the formal study and during the first study period if deemed necessary by the prescribing physician.

At the inception of this trial a clinical examination was performed, as well as a set of biochemical measurements (serum creatinine, potassium, sodium and 24-h urinary sodium), using an »AU 600 Olympus« chemistry analyzer. Body height and weight were measured by using a physician decimal scale with a sliding counterweight and a height rod »Detecto 2391« (USA). Dominant arm BP was measured with a mercury sphygmomanometer, taking the mean of the last two of three consecutive readings in the supine, sitting and standing positions, and 30-min ambulatory BP monitoring was performed with »VSM Medech Ltd. Model BPM-100« (Vancouver, Canada) automated recorder[3].

The same measurements were repeated after each month of the study. Results were compared between and within the study groups. Here we present the blood pressure recordings in the seated position as mean arterial pressure (MAP) changes, as well as body weight, serum creatinine, potassium and sodium levels, 24 h urinary output and sodium excretion. The obtained data was tabulated, presented as means and standard deviations (±SD), and statistically evaluated using the software package »SPSS 11.5«, Chicago, Illinois. Significance of the observed differences was assessed using the paired and unpaired t-test and the analysis of variance (ANOVA). A p value of <0.05 was regarded as significant; the p values were corrected for multiple testing with the Bonferroni adjustment.

Results

A total of 110 examinees, 49 males (44.5%) and 61 females (55.5%), were enrolled in the study. The intervention group included 60 (54.6%) and the control group 50 (45.4%) patients. The intervention group patients were allocated in 4 equal subgroups: 15 were taking lisinopril/hydrochlorothiazide with ibuprofen (L/H±IB), and 15 with piroxicam (L/H±PX); 15 were taking amlodipine with ibuprofen (AM±IB), and 15 with piroxicam (AM±PX). The control group was divided in two subgroups: 25 examinees were taking lisinopril/hydrochlorothiazide and 25 amlodipine only (Table 1). There were no significant differences between the intervention and control subgroups concerning age ($p=0.90$), gender ($p=0.653$) or prescribed drugs ($p=0.338$). The average daily dosage was 18.0±4.5/11.3±2.8 mg for lisinopril/hydrochlorothiazide, 6.9±2.4 mg for amlodipine, 1154±348 mg for ibuprofen, 16.9±4.8 mg for piroxicam, and 2490±429 mg for paracetamol; the individual doses were held constant during the study phases.

Mean arterial pressure (MAP) in the L/H±IB subgroup changed significantly during this study (Table 2): the introduction of ibuprofen brought about a marked increase by 8.9% (9.5 mm Hg; $p<0.001$); its withdrawal during the paracetamol phase resulted in a decrease almost to the baseline values, and reintroduction of ibuprofen was followed by a 7.5% increase in MAP ($p=0.003$). In the L/H±PX subgroup similar, even more pronounced changes were registered: during the piroxicam phase MAP increased from baseline by 9.5% (10.2 mm Hg; $p<0.001$), during paracetamol it returned to mere 0.6% above baseline ($p>0.5$), and when piroxicam was reintroduced MAP increased again by 7.9% ($p<0.001$). In the AM±IB and AM±PX subgroups the between-phase MAP deviations were minor and insignificant.

Body weight (Table 3, Figure 1) increased significantly in L/H±PX subgroup only (from 79.6±13.4 kg to 81.5±14.0 kg or +1.9 kg; $p=0.028$). Plasma creatinine

TABLE 2
MEAN ARTERIAL PRESSURE CHANGES VS. BASELINE DURING IBUPROFEN, PIROXICAM OR PARACETAMOL

Antihypertensive	L/H	AM
NSAID	Absolute (and percentual) changes	
IB (mm Hg)	+9.5 (8.9%)***	+0.5 (0.5%)
PX (mm Hg)	+10.2 (9.5%)***	+0.5 (0.5%)
PA (mm Hg)	+1.4 (1.3%)	+0.2 (0.2%)

***p<0.001, AM – amlodipine, IB – ibuprofen, L/H – lisinopril/hydrochlorothiazide, PA – paracetamol, PX – piroxicam

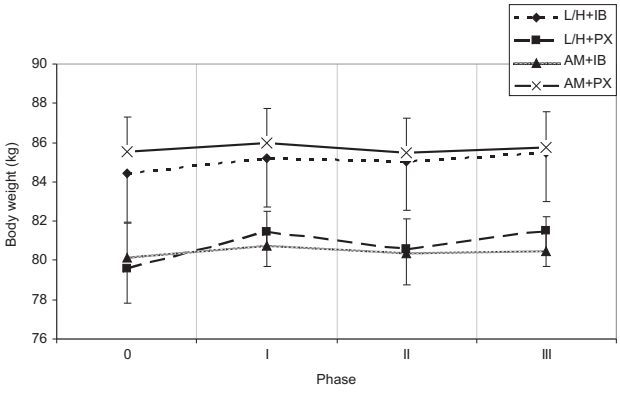

Fig. 1. Body weight changes during the study periods (error bars showing standard deviations of the data). AM – amlodipine, IB – ibuprofen, L/H – lisinopril/hydrochlorothiazide, PX – piroxicam.

TABLE 3
BODY WEIGHT, PLASMA CREATININE, POTASSIUM, SODIUM, DIURESIS, AND 24 H URINARY SODIUM ALTERATIONS VS. BASELINE

Study group	Control		Intervention					
	L/H	AM	L/H+IB	L/H+PA	L/H+PX	AM+IB	AM+PA	AM+PX
Parameter	Absolute (and percentual) changes							
Body weight (kg)	–0.2 (↓0.2%)	+0.1 (0.1%)	+0.7 (0.9%)	+0.5 (0.6%)	+1.9 (2.3%)*	+0.6 (0.8%)	+0.2 (0.2%)	+0.5 (0.5%)
Creatinine (mg/dL)	+0.9 (1.0%)	–5.6 (↓5.7%)	+3.0 (3.3%)	+4.5 (4.9%)	+0.6 (0.6%)	+1.2 (1.3%)	+1.5 (1.7%)	+2.0 (2.6%)
Potassium (mmol/L)	0.0 (0%)	+0.1 (2.2%)	0.0 (0%)	0.0 (0%)	+0.2 (5.3%)	+0.1 (0.4%)	0,0 (0%)	–0.1 (↓1.5%)
Sodium (mmol/L)	–0.1 (↓0.1%)	+0.1 (0.1%)	+0.4 (0.3%)	+0.3 (0.2%)	0.0 (0%)	+1.6 (1.1%)	+0.4 (0.3%)	–0.2 (↓0.1%)
Urinary volume (mL/24 h)	+56.2 (3.0%)	+838.3 (49.4%)**	–161.6 (↓10.8%)	–12.9 (↓0.9%)	–152.5 (↓8.8%)	–442.0 (↓21.1%)	+15.1 (0.7%)	+48.6 (3.5%)
24 h urinary Na^+ (mmol)	–6.1 (↓3.1%)	+12.7 (7.5%)	+9.0 (4.9%)	–2.1 (↓1.2%)	+8.8 (5.1%)	–4.4 (↓1.9%)	–11.6 (↓5.0%)	–15.2 (↓8.6%)

**p=0.028, **p=0.003, AM – amlodipine, IB – ibuprofen, L/H – lisinopril/hydrochlorothiazide, PA – paracetamol, PX – piroxicam

values (Table 3) did not change significantly in any of the groups, though they displayed an increasing trend. Plasma potassium concentrations (Table 3), displayed an increasing trend (e.g. +5.3% in the L/H±PX subgroup), but the changes were insignificant in all of the groups ($p > 0.15$). Plasma sodium concentrations in both lisinopril/hydrochlorothiazide subgroups remained the same, while insignificant changes occurred in the amlodipine subgroups (Table 3). Sodium excretion in 24 h urine was 4.9% higher in the L/H±IB subgroup compared to the baseline (Table 3), 5.1% higher in the L/H±PX subgroup and lower in both of the amlodipine subgroups (1.9% in AM±IB and 8.6% in AM±PX). These changes were not statistically significant either ($p > 0.25$). The volume of 24 h urine in the intervention group did not change significantly during this study. Urinary output was reduced by 10.8% in the L/H±IB subgroup, 8.8% in the L/H±PX subgroup and 21.1% in the AM±IB subgroup, but increased by 3.5% in the AM±PX subgroup (Table 3). All of these changes were insignificant ($p > 0.25$). However, a significant increase in diuresis was registered in the control amlodipine group after the first phase (from 1696.0± 548.9 mL to 2534.3±693.6 mL or +838.3 mL; $p = 0.003$).

There were no drop-outs from this study. Some minor and expected side-effects were noted in the amlodipine group only: 9 examinees had ankle edema (4 of them in the intervention group and 5 in the control group), but none withdrew from the study. NSAID-related side-effects were noted in 3 examinees in the piroxicam subgroups (mild gastrointestinal symptoms).

Discussion

Our trial has confirmed that ibuprofen and piroxicam significantly reduce the antihypertensive effects of lisinopril/hydrochlorothiazide combination, while paracetamol was almost inert in this respect. On the other hand, adding ibuprofen or piroxicam does not influence amlodipine's antihypertensive activity[3].

Body weight during NSAID intake did not change appreciably, except in the L/H±PX subgroup (+1.9 kg). Other investigators have obtained discordant results: some showed a significant increase, while others did not[5–10]. Klassen et al. have reported a significant increase in body weight during naproxen intake[7], while Radack et al. did not observe body weight gain with either ibuprofen or paracetamol[10]. Such increment, reflecting fluid retention and plasma volume expansion, is usually short-term, happens during the first week of NSAID therapy and usually does not surpass 2 kg[11,12]. Creatinine levels and urine volume did not change appreciably in this study, which is congruent to other reports[5,6]. According to a meta-analysis done by Johnson et al.[13], sodium and fluid retention does not seem to be the leading cause of prohypertensive NSAID activity, since body weight and sodium values did not change with NSAIDs and diuretics were not superior to other antihypertensives. Although our results support that point of view, the prohypertensive mechanisms of NSAIDs are still unresolved.

Most published trials were investigating pure NSAIDs – ACE inhibitors interaction while, in this study, the examinees were taking a fixed combination of an ACE inhibitor, lisinopril, and a diuretic, hydrochlorothiazide[5,6,8,14]. That combination in concert with NSAIDs did not lead to significant serum potassium elevation, except in the L/H± PX subgroup. In another study, indomethacin increased serum potassium level among hypertensive subjects treated with enalapril (more) and felodipine (less), while a subsequent investigation by the same authors has not found a significant change (indomethacin with amlodipine or enalapril)[5,6].

Sodium values did not change significantly in our trial, but there was a slight difference between the intervention and the control amlodipine group. The baseline natriuria was quite high, presumably due to inadequate diet (too high salt intake; around 12 g/day or 200 mmol Na/day). In either lisinopril/hydrochlorothiazide or amlodipine subgroups, the addition or exclusion of NSAIDs did not bring about a statistically significant change in the 24h urine sodium excretion. In another study[15], NSAIDs did not decrease natriuresis in examinees treated with lisinopril and hydrochlorothiazide. In the Polonia et al. paper[8], indomethacin caused a significant drop in natriuria among hypertensives treated with enalapril, but also among those receiving nifedipine. In the study, performed by Krekels et al., a daily dose of 20 mg nitrendipine caused a significant natriuretic effect independent of it's hemodynamic activity[16].

Prohypertensive effects of NSAIDs in their interaction with antihypertensives depend on the relative role the prostaglandins play in hypotensive activity of each drug, i.e. on the importance of prostaglandin inhibition in a particular blood pressure-lowering effect[13]. Decreased synthesis of natriuretic prostaglandins (PGE_2) enhances sodium retention by lowering saluresis. Thus, during the NSAID phases in our experiment, there was less natriuresis expected in lisinopril/hydrochlorothiazide than in amlodipine subgroups. However, no significant changes in 24 h urinary sodium excretion were observed.

Blood pressure increase in lisinopril/hydrochlorothiazide intervention subgroups was not accompanied by body weight increase and/or decrease in urinary sodium excretion, suggesting that vasoconstriction, instead of volume expansion, is the dominant mechanism of blood pressure increase in hypertensive patients taking concomitant NSAIDs. Inhibition of vasodilatory prostaglandin synthesis is apparently the main cause of prohypertensive NSAID activity; prostacyclin is a strong vasodilator and abating its synthesis increases peripheral resistance. In addition, NSAIDs reduce endothelial emission of nitric oxide (NO) and increase renal endothelin synthesis (ET-1), which is a highly potent vasoconstrictor. ET-1 does not only increase peripheral vascular resistance but stimulates sodium and water retention as well[17]. We found that fluid retention was less important than vasoconstriction, but we did not perform measurements of ET-1, renin or angiotensin II. A correlation between plasma ET-1 and NO concentrations and arterial pressure has been found in diabetic patients receiving ACE inhibitors[18]. More pronounced hypertensive effect of NSAIDs in diabetic nephropathy could be explained with higher ET-1 levels due to earlier endothelial activation, even before the onset of microalbuminuria[18]. ET-1 receptors in endothelial cells are connected to voltage calcium channels by G proteins[19]. That might explain why calcium antagonists ameliorate endothelin induced vasoconstriction; in addition to calcium channels, they block ET-1 receptors as well.

COX-2 is involved in water and electrolyte homeostasis, while COX-1 is mostly active in vascular endothelium[1]. Prostaglandins mediated by COX-1 and COX-2 seem to have opposite hemodynamic effects. COX-2 inhibition enhances and prolongs the pressor effect of angiotensin II, whereas COX-1 inhibition works the opposite way. Several NSAIDs have been shown to inhibit COX-2 more than COX-1[20]. According to a report, COX-1/COX-2 inhibition ratio was 0.12 for ketoprofen, 0.32 for ASA, 0.59 for ibuprofen, 1.27 for piroxicam and 7.93 for etodolac[21]. In our study, piroxicam was more prohypertensive than ibuprofen, which may be explained with this selectivity difference. Paracetamol had little effect on blood pressure control, presumably because its minor effect on peripheral prostaglandin synthesis[22].

There are some limitations of this study. It was not double blind but open, with the prescriber physician unaware of the results and the assessor physician unaware of the prescribed drugs. Because of ethical reasons (severity of osteoarthritis), a placebo group was not included. Instead, the examinees were given paracetamol during the wash-out interval between two NSAID periods (which did not worsen the blood pressure control and proved to be comparable to placebo).

A dose-response curve can not be extrapolated from this study either. Since the patients were titrated to the best antihypertensive and analgesic effect, it may be assumed that the doses of drugs used were individually equipotent and comparable to those prescribed in clinical practice.

The number of suitable patients willing to participate (110 out of possible 223 or 49.3%) and the relatively small sample size limits the power to prove possibly relevant differences between ibuprofen and piroxicam concerning blood pressure control. Low number of diabetic and renal patients prevented the assessment of co-morbidity role in these interactions. Hypertensive patients with plasma creatinine levels above 150 μmol/L were not included in this study and our results cannot be extrapolated to patients with renal failure.

On the other hand, the study was prospective, randomized, controlled, with parallel and cross-over comparison, performed in real conditions of a busy family practice.

The clinical relevance of its results lies in the individuation of best tolerated combinations of antihypertensive and antirheumatic drugs for hypertensive persons with rheumatic deseases.

Conclusion

This study confirmed the unfavorable interaction between some antihypertensives and NSAIDs. Much better hypertension control was achieved while taking paracetamol instead of ibuprofen or piroxicam. Reintroduction of one of those NSAIDs was followed by a significant increasse in blood pressure. Since body weight, serum creatinine, potassium, sodium, urinary output and uri-

nary sodium excretion did not change noticeably during the trial, it seems that NSAID's untoward effects on hypertension control are mainly due to vasoconstriction and much less to volume expansion.

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PROHIPERTENZIVNO DJELOVANJE NESTEROIDNIH ANTIREUMATIKA JE PRETEŽNO UZROKOVANO VAZOKONSTRIKCIJOM

SAŽETAK

Nesteroidni antireumatici (NSAR) pokazuju prohipertenzivna svojstva i smanjuju učinke mnogih antihipertenziva. Mehanizam ovih interakcija još uvijek nije dovoljno objašnjen. Cilj ovog istraživanja bio je: odrediti razinu prohipertenzivnog djelovanja dva NSAR-a (ibuprofen, piroksikam) i paracetamol, uzimana istodobno s dva antihipertenziva (kombinacija lizinopril/hidroklorotiazida i amlodipin) i pridonijeti razumijevanju ove interakcije. U prospektivno ispitivanje provedeno u ordinaciji obiteljske medicine bilo je uključeno 110 liječenih hipertoničara u dobi od 56–85 godina; 50 u kontrolnu i 60 u interventnu skupinu (uzimali i NSAR zbog artroze). Antihipertenzivna terapija nije se mijenjala tijekom liječenja, dok je uzimanje NSAR nasumično podijeljeno u 3 jednomjesečna razdoblja: faza I – puna doza propisanog lijeka, faza II – bez NSAR (daje se paracetamol), faza III – ponovno isti antireumatik, u istoj dozi. Nakon svakog jednomjesečnog razdoblja mjeren je arterijski tlak, tjelesna masa, vrijednosti kreatinina, kalija i natrija u plazmi, diureza i vrijednosti natrija u 24 h urinu. U lizinopril/hidroklorotiazid podskupini kako ibuprofen tako i piroksikam podigli su srednji arterijski tlak za 8,9–9,5% ($<0,001$). Značajan porast tjelesne mase nađen je samo u lizinopril/hidroklorotiazid + piroksimam podskupini. Vrijednosti kreatinina, kalija, natrija, diureze i natrija u 24 h urinu nisu se značajno mijenjale. Budući da nisu opažene osjetne promjene tjelesne mase, prometa vode ni elektrolita, mehanizam prohipertenzivnog djelovanja NSAR je, čini se, pretežno vazokonstrikcijski.