

INTERACTION BETWEEN ANTIHYPERTENSIVES AND NSAIDS IN PRIMARY CARE: A CONTROLLED TRIAL

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ABSTRACT

Background

Non-steroidal anti-inflammatory drugs (NSAIDs) may increase blood pressure (BP) and blunt the effects of many antihypertensives. It seems that NSAIDs and the antihypertensive drugs differ in their propensity to such an interaction.

Objectives

To determine the extent of the interaction between two antihypertensives and three NSAIDs.

Methods

A prospective clinical trial in a family practice included 88 treated hypertensives aged over 55 years; 39 controls and 49, also taking NSAIDs for osteoarthritis. During this 3-month study, two antihypertensives, lisinopril/hydrochlorothiazide and amlodipine, were compared with three NSAIDs: ibuprofen, acetaminophen, and piroxicam. BP was measured with standard mercury sphygmomanometer and with an automatic device, in standing, sitting, and supine position.

Results

The average starting blood pressure in the study group was $149.3 \pm 9.8/88.6 \pm 6.8$ mm Hg. In the lisinopril/hydrochlorothiazide subgroup, both ibuprofen and piroxicam elevated systolic BP by 7.7-9.9% ($p < 0.001$), which, during the acetaminophen period, decreased by 6.9-9.4% to 0.3-0.9% above baseline ($p < 0.001$), increasing again by 7.0-7.7% ($p < 0.001$) during the second exposition to these drugs. In the amlodipine subgroup, ibuprofen or piroxicam increased BP by 1.1-1.6% ($p > 0.290$) only, and there were no significant shifts in the follow-up periods. Analogous deviations were observed with both measurement devices, in all the examinee's positions. In the control group, BP did not change appreciably.

Conclusions

Piroxicam and ibuprofen markedly blunt the effects of antihypertensive drugs while acetaminophen is almost inert. Lisinopril/hydrochlorothiazide combination is much more affected by this interaction than amlodipine (ClinicalTrials.gov #NCT00631514).

Key words: *Antihypertensive drugs; family practice; interaction; non-steroidal anti-inflammatory drugs*

(see Editorial letter Can J Clin Pharmacol Vol 15(3) Fall 2008:e383-e384; October 24, 2008)

Arterial hypertension is the most important preventable cause of premature death and disability. Although its treatment is very effective and well tolerated, the practical achievements leave much to be desired for two main reasons: inadequate medication (noncompliance, inappropriate pres-

ription) and interferences (untoward life style, comedication with prohypertensive agents, pharmacokinetic and/or pharmacodynamic drug interactions).¹ Indeed, the blood pressure control may be markedly blunted by concomitant intake of prohypertensive drugs, such as cocaine,

cyclosporine or erythropoietin, but of major concern is coprescription of NSAIDs, since the interactive potential of these two drug classes is huge due to high prevalence of both hypertension and osteoarthritis: such a comorbidity is seen in 15-26% of elderly patients from different populations.¹

The prohypertensive effects of NSAIDs presumably depend on several mechanisms. Their analgesic and antiinflammatory effects are mostly derived from cyclooxygenase (COX) inhibition and consequent decrease in prostaglandin synthesis. There are at least two, genetically, functionally and structurally different moieties of this enzyme: constitutive (COX-1) and inducible (COX-2). COX-1 is permanently active in many bodily structures, regulating normal tissue activities, while COX-2 is activated by inflammation, trauma or infection. Its inhibition leads to decreased PGI₂ production in the vascular endothelium, with no change in TxA₂ synthesis in the platelets, predisposing to vasoconstriction, thrombosis and endothelial lesion. Moreover, all NSAIDs impede physiological prostaglandin synthesis in the kidneys resulting in fluid retention and local vasoconstriction.¹

For all NSAIDs, a more or less pronounced prohypertensive effect has been described in many interventional and observational studies⁴⁻¹⁹, in meta-analyses²⁰⁻²², and in review papers²³⁻²⁹ (for the sake of brevity quoted are just the most prominent out of more than 100 references). From this heterogeneous data (the studies were prospective and retrospective, with highly variable numbers of examinees, with or without placebo control, parallel or crossover etc.) a vague conclusion results that, among the antihypertensive agents, calcium channel blockers could be less susceptible to this untoward interaction than diuretics, beta-adrenergic blockers or ACE inhibitors^{8-10,15,17}, and that some NSAIDs could be more prohypertensive (ibuprofen, indomethacin, naproxen, piroxicam, rofecoxib) than others (acetaminophen, acetylsalicylic acid, celecoxib, ketoprofen, sulindac).^{3-8,11-17,20-29}

To test the hypothesis that some NSAIDs are more prone to elevate blood pressure than the others, and that some antihypertensives are more susceptible, and others more resistant to this interaction, we have designed a prospective,

controlled trial in a primary care (family practice) office in Split, Croatia, taking care of some 1,600 adult patients.

MATERIALS AND METHODS

This factorial, parallel group, prospective study enrolled already treated hypertensives (taking amlodipine or lisinopril/hydrochlorothiazide fixed combination) of either gender, aged >55 and <76 years. Informed consent was obtained and the Split University School of Medicine Ethical Committee approved the study. The investigation was registered with *ClinicalTrials.gov* and received PRS #NCT00631514.

The intervention group included persons with concomitant osteoarthritis of the hip or knee, requiring regular intake of NSAIDs (at least one defined daily dose per day in the preceding month). The control group included hypertensive patients with the same demographic characteristics, but not requiring NSAIDs (Table 1). Patients unable to tolerate withdrawal of their osteoarthritis therapy, those unwilling to participate and uncooperative persons were not included. Following clinical work-up and discontinuation of NSAIDs for at least 3 days (the run-in period lasted 3-7 days only), the examinees with osteoarthritis already taking amlodipine (5-10 mg o.d.) or lisinopril/hydrochlorothiazide fixed drug combination (10/6.25-20/12.5 mg o.d.) were randomized (sealed envelopes containing advanced drug prescription) into two experimental arms, to take either ibuprofen (400-600 mg t.i.d.) or piroxicam (10-20 mg o.d.) for one month, followed by acetaminophen (1000 mg t.i.d.) during the second month as a "wash-out" interval, and resuming the assigned NSAID (ibuprofen or piroxicam) during the third month of the study (Figure 1). The control examinees (hypertensives with no osteoarthritis) continued with their current antihypertensive therapy. That group was included to identify and adjust for possible confounding variables (e.g., seasonal variations in ambient temperature or in salt ingestion).

In other words, each patient in the intervention group underwent 3 study periods (phases) of 1 month duration each, taking the allotted antihypertensive all the time but switching from the assigned NSAID after the first phase to acetaminophen during the second phase and

resuming the first NSAID in the third phase. Since the formulations of the study drugs were not identical, and the dosages were different, it was a single blind study, in which the assessor physician (I.P.) was unaware of the patients' allocation, performed by the assigner physician (M.K.).

In addition to general demographic quantification, arterial pressure was measured in the morning, between 9 and 10 a.m., with the standard mercury sphygmomanometer according to standard recommendations, registering the mean of the last two of three consecutive readings in the supine, sitting and standing position, and with the automated blood pressure recorder Model BPM-100, "VSM MedTechLtd." (Vancouver, Canada), taking the mean of the last five of six consecutive readings in seated position obtained in 5 min intervals over 30 min, at the inception (*phase 0; baseline*), and at the end (i.e. on one of the period's last two mornings) of the first (*phase I*), of the second (*phase II*), and of the third study month (*phase III*).

Standing blood pressure recorded with the mercury instrument was designated as the primary outcome of the trial because taking blood pressure in the erect position best detects the undesired

orthostatic hypotension, particularly troublesome in an elderly, friable person (all our patients were over 55 years of age), and the mercury device is still the clinical standard, especially in family practice.

Additional measurements were performed (e.g., body weight, serum creatinine, sodium and potassium; 24 h urinary sodium), which will not be considered in detail in this report. Expecting a minimal relevant difference of 8 mm Hg in systolic blood pressure between the more "prohypertensive" NSAIDs (piroxicam, ibuprofen) and more inert agents in this respect (acetaminophen), and accepting a two-sided α error of 0.05, we had to enroll at least 20 examinees per group to achieve a power of 80%.

The results are presented as means, standard deviations (*SD*) and 95% confidence intervals (*CI₉₅*); statistical significance was assessed using analysis of variance (*ANOVA*), unpaired *t* test or χ^2 test, as appropriate, employing the SPSS software package, version 11.5 (SPSS, Chicago, Illinois). The *p* values were corrected for multiple testing with the Bonferroni adjustment; a *p* value <0.05 was regarded as significant.

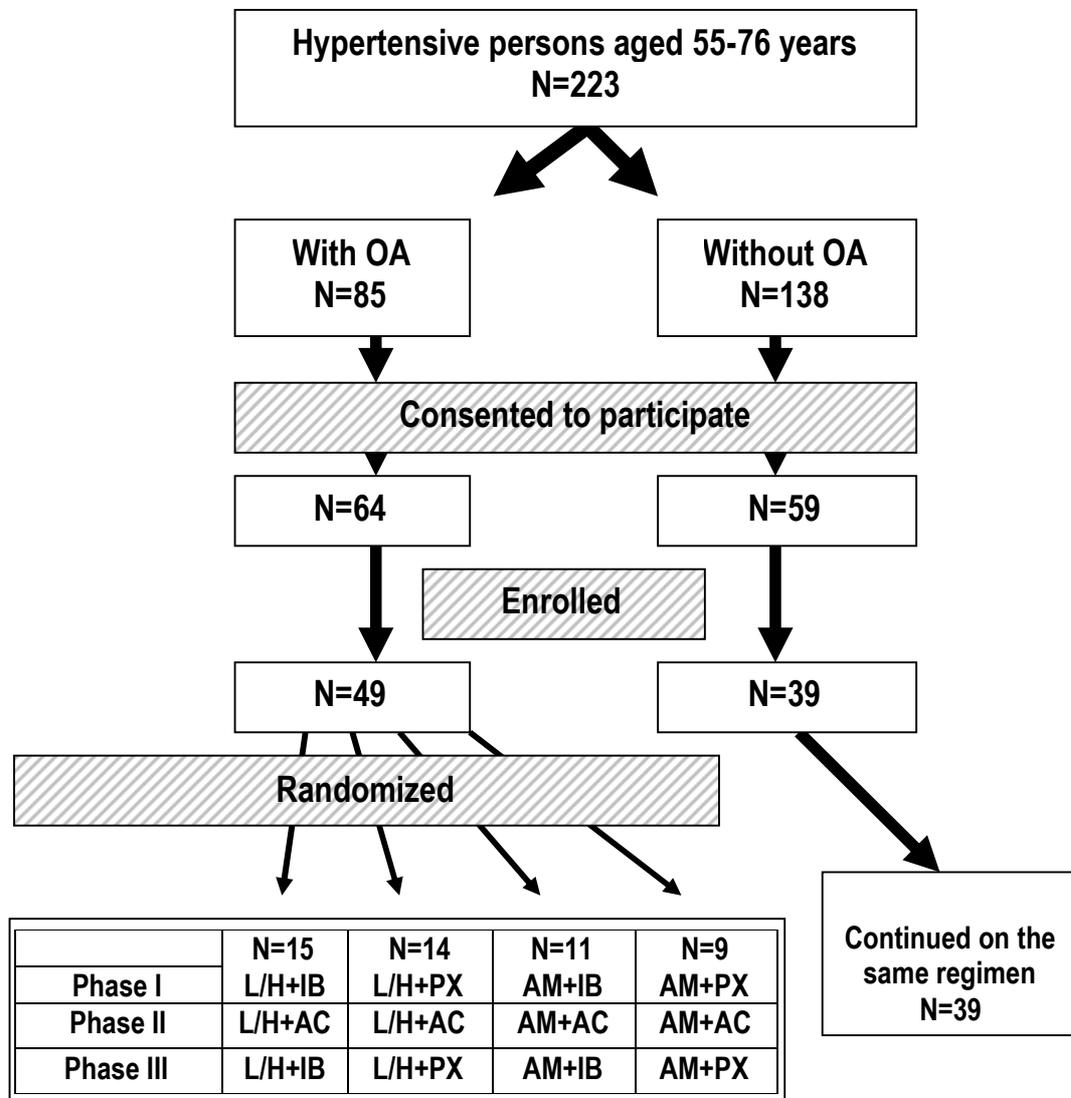
TABLE 1 Baseline characteristics of the examinees

Study group Parameter	Control L/H	Control AM	Intervention L/H±IB	Intervention L/H±PX	Intervention AM±IB	Intervention AM±PX
Randomized (n)	22	17	15	14	11	9
Male/female (n)	12/10	10/7	7/8	5/9	2/9	2/7
Age (years; mean ±SD)	68.3±5.5*	68.7±8.2	70.5±7.2	69.9±7.6	69.6±6.3	69.4±8.8
Weight (kg; mean ±SD)	82.1±11.6	81.7±14.2	84.4±15.7	78.1±12.6	80.1±13.9	87.3±16.7
Standing systolic BP (mm Hg)	149.5±11.4	147.0±9.9	144.9±9.3	148.9±13.0	152.9±6.5	153.1±5.8
Standing diastolic BP (mm Hg)	90.0±8.3	89.5±5.6	87.7±6.7	88.9±5.4	87.6±9.2	90.4±6.4

*Means ± standard deviations of the data

Acronyms: AM= amlodipine; IB= ibuprofen; L/H= lisinopril/hydrochlorothiazide; PX= piroxicam.

FIG. 1 Flowchart showing the study inclusions, exclusions and final sample size



AC= acetaminophen; AM= amlodipine; IB= ibuprofen; L/H= lisinopril/hydrochlorothiazide; OA= osteoarthritis; PX= piroxicam.

None of the randomized subjects was lost to follow-up, and all 88 were analysed.

RESULTS

There were all in all 88 examinees; 38 males (43.2%) and 50 females (56.8%), 49 of whom (55.7%) were in the intervention, and 39 (44.3%) in the control groups. In the control group there were 17 women and 22 men, aged 68.5 ± 6.7 years, weighting 82.0 ± 12.4 kg, and their standing BP at

the inception of this study was $148.6 \pm 10.6 / 89.2 \pm 7.1$ mm Hg; 22 (56.4%) of the control subjects were taking lisinopril/hydrochlorothiazide, and 17 (43.6%) amlodipine only.

The intervention group patients were allocated in 4 subgroups: 15 (30.6% of them) were taking lisinopril/hydrochlorothiazide with ibuprofen, and 14 (28.6%) with piroxicam; 11

(22.4%) were taking amlodipine with ibuprofen, and 9 (18.4%) with piroxicam.

The mean age of the intervention group (Table 1) was 69.8±6.9 years; 69.4±7.2 for the female, and 70.1±6.8 years for the male examinees, not differing significantly between the subgroups or towards the control group (one-way ANOVA: $F_{5,82}=0.220$; $p=0.95$ and $F_{1,86}=0.043$, $p=0.83$, respectively). The average sitting blood pressure, 148.9±10.2 / 89.1±6.9 mm Hg, did not differ significantly between the study subsets (ANOVA: $F_{1,86}=1.982$; $p=0.142$). The same was true for the average heart rate (75.2±9.3 bpm), body weight (81.8±13.0 kg), serum creatinine (92.8±20.2 µmol), serum potassium (4.54±0.48 mmol/l) or 24 h urinary sodium excretion (189.3±86.6 mmol). The average daily drug dosages were 18.0±4.5/11.3±2.8 mg for lisinopril/hydrochlorothiazide combination, 6.9±2.4 mg for amlodipine, 1154±348 mg for ibuprofen, 16.9±4.8 mg for piroxicam, and

1490±429 mg for acetaminophen; the individual doses were held constant during the study.

Standing systolic blood pressure (SBP) variations during this study are shown in Table 2. The observed differences in the control group did not reach statistical significance during the study (ANOVA: $F_{3,63}=0.061$; $p=0.980$), while in the intervention group, there were several substantial changes. In the lisinopril/hydrochlorothiazide subgroup assigned to ibuprofen, there were significant between-phase deviations (ANOVA: $F_{3,42}=7.710$; $p<0.001$; $\eta^2=0.355$). The average baseline SBP in phase I increased by 7.7% (+11.2 mm Hg; $CI_{.95}$ 6.1-16.5 mm Hg; $p=0.004$), decreased in phase II by 6.9% (-10.8 mm Hg; $CI_{.95}$ 5.2-16.4 mm Hg; $p=0.013$), and increased again in phase III by 6.7% (+9.7 mm Hg; $CI_{.95}$ 3.3-16.2 mm Hg; $p=0.051$). A significant interaction effect between the study phase and experimental subgroup (ANOVA: $F_{2,68}=3.770$; $p=0.028$; $\eta^2=0.1$) was found.

TABLE 2 Standing systolic blood pressure changes during the study periods

Period	Control L/H	Control AM	Intervention L/H+IB	Intervention L/H+PX	Intervention AM+IB	Intervention AM+PX
Phase 0 (baseline)	149.5±11.4	147.0±9.9	144.9±9.3	148.9±13.0	152.9±6.5	153.1±5.8
Phase I	149.4±14.9	147.2±13.2	156.1±12.6 *	162.9±17.6 **	155.3±7.1	154.8±9.2
Phase II	148.5±14.6	149.2±12.9	145.3±14.7	147.6±14.6	155.6±9.6	153.2±8.7
Phase III	149.1±11.5	146.8±12.8	155.0±12.9	160.4±14.8 *	151.7±5.0	152.0±12.0

Means ± standard deviations of the data

* $p=0.021-0.040$; ** $p=0.001-0.020$

Acronyms: AM= amlodipine; IB= ibuprofen; L/H= lisinopril/hydrochlorothiazide; PX= piroxicam.

In the lisinopril/hydrochlorothiazide subgroup assigned to piroxicam, the same changes were even more pronounced and the between-phase deviations were highly significant (ANOVA: $F_{3,36}=9.986$; $p<0.001$; $\eta^2=0.454$). The average SBP in phase I increased by 9.5% (+14.1 mm Hg; $CI_{.95}$ 6.6-20.8 mm Hg; $p=0.001$), decreased in phase II by 9.4% (-13.3 mm Hg; $CI_{.95}$ 7.0-20.3 mm Hg; $p=0.004$), and increased again in phase III by 8.0% (+9.7 mm Hg; $CI_{.95}$ 5.2-14.5 mm Hg; $p=0.030$).

Taking these two subgroups together, the global effect of ibuprofen or piroxicam addition was even stronger (ANOVA: $F_{3,81}=18.058$; $P=0.003$; $\eta^2=0.401$), while SBP changes in the

control group were tiny (ANOVA: $F_{3,63}=0.061$; $P=0.980$).

The calcium channel blocker subgroups did not show such outcomes. In the amlodipine examinees assigned to ibuprofen, the between-phase blood pressure deviations were minor (ANOVA: $F_{3,27}=1.303$; $p=0.294$), and the differences between the intervention and the control group were insignificant (ANOVA: $F_{2,46}=0.883$; $p=0.421$). The increase in SBP between phase 0 and phase I was 1.5% (+2.4 mm Hg; $CI_{.95}$ ranging from -4.9 to +10.3 mm Hg). In the amlodipine subgroup randomized to piroxicam, the between-phase deviations were even less

(ANOVA: $F_{3,24}=0.206$; $p=0.891$), insignificant in comparisons with the control group (ANOVA: $F_{2,44}=0.257$; $p=0.774$), and did not change during the acetaminophen interval. Comparing both lisinopril/hydrochlorothiazide subgroups taking either ibuprofen or piroxicam ($n=29$) to those taking amlodipine under the same conditions ($n=20$), the observed differences were remarkable (e.g. *t*-test in period II: $t=2.605$; $CI_{.95}=1.815-14.18$; $df=47$; $p=0.0123$).

Similar results were obtained with the diastolic blood pressure (DBP; Table 3), which

did not fluctuate significantly in the control group (ANOVA: $F_{3,48}=2.039$; $p=0.121$).

In the lisinopril/hydrochlorothiazide subgroup randomized to ibuprofen, significant between-phase variations were noted (ANOVA: $F_{3,42}=10.403$; $p<0.001$; $\eta^2=0.426$): an increase in phase I by 8.6% (+7.6 mm Hg; $CI_{.95}=2.2-13.4$ mm Hg; $p=0.022$), a decrease in phase II by 7.0% (-6.7 mm Hg; $CI_{.95}=1.9-11.7$ mm Hg; $p=0.027$), and another increase in phase III by 6.4% (+5.7 mm Hg; $CI_{.95}=1.8-9.4$ mm Hg; $p=0.031$).

TABLE 3 Standing diastolic blood pressure changes during the study periods

Period	Control L/H	Control AM	Intervention L/H+IB	Intervention L/H+PX	Intervention AM+IB	Intervention AM+PX
Phase 0 (baseline)	90.0±8.3	89.5±5.6	87.7±6.7	88.9±5.4	87.6±9.2	90.4±6.4
Phase I	90.9±7.7	90.2±7.1	95.3±6.6 **	95.8±9.9*	86.8±7.7	92.1±8.8
Phase II	89.4±8.8	92.8±8.1	88.6±7.5	89.6±10.4	86.5±9.7	91.9±8.3
Phase III	92.3±7.1	89.4±8.0	94.3±9.1 **	95.4±11.4	89.4±8.3	92.8±7.3

Means ± standard deviations of the data

* $p=0.021-0.040$; ** $p=0.001-0.02$

Acronyms: AM= amlodipine; IB= ibuprofen; L/H= lisinopril/hydrochlorothiazide; PX= piroxicam.

The mean DBP among the lisinopril/hydrochlorothiazide examinees assigned to piroxicam showed similar variations (ANOVA: $F_{3,33}=4.448$; $p=0.010$; $\eta^2=0.288$); it increased in phase I by 7.0% (+6.2 mm Hg; $CI_{.95}=2.5-9.9$ mm Hg; $p=0.025$), decreased in phase II by 5.4% (-5.2 mm Hg; $CI_{.95}=1.3-9.3$ mm Hg; $p=0.039$), and increased again in phase III by 5.3% (+5.8 mm Hg; $CI_{.95}=1.9-9.4$ mm Hg; $p=0.042$). DBP variability in the amlodipine group was minor (ANOVA: $F_{3,30}=1.891$; $p=0.152$), and was not significantly influenced by the addition of ibuprofen (*t*-test: $t=-1.20$; $df=9$; $p=0.300$). Introduction or withdrawal of piroxicam did not induce appreciable DPB changes within the amlodipine subgroup (ANOVA: $F_{3,15}=0.342$; $p=0.796$) nor in comparison to the control group (ANOVA: $F_{2,28}=1.736$; $p=0.195$).

Longitudinal comparison of DBP changes in the four intervention subgroups showed significant fluctuations (ANOVA: $F_{2,80}=4.018$; $p=0.022$; $\eta^2=0.091$), much more pronounced in the lisinopril/hydrochlorothiazide group (ANOVA:

$F_{3,78}=14.633$; $p<0.001$; $\eta^2=0.360$) than in the amlodipine group (ANOVA: $F_{3,45}=0.757$; $p=0.524$). DBP differences between the two lisinopril/hydrochlorothiazide subgroups taking NSAIDs were minor (ANOVA: $F_{2,80}=0.205$; $P=0.815$).

Comparable blood pressure changes were observed in the supine and sitting position (not shown), and with automatic blood pressure recording (Table 4). Automated readings, less influenced by bias, were consistently lower than the sphygmomanometric ones by some 10 mm Hg systolic, and some 7 mm Hg diastolic, as expected.

The relative, percentual, changes in systolic BP during this study are presented in Figure 2. A sharp increase in phase I and III is clearly seen in the lisinopril/hydrochlorothiazide subgroups taking ibuprofen or piroxicam, while in the amlodipine subgroups or in phase II (acetaminophen), the baseline values did not vary substantially.

TABLE 4 Automatically recorded sitting systolic blood pressure changes during the study periods

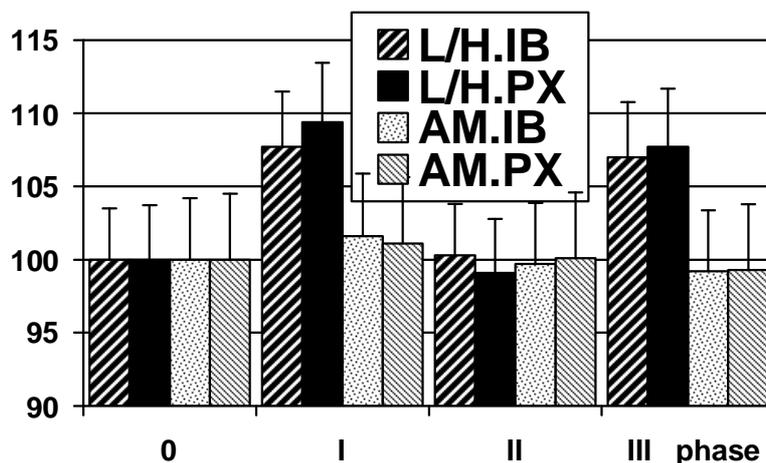
Period	Control L/H	Control AM	Intervention L/H±IB	Intervention L/H±PX	Intervention AM±IB	Intervention AM±PX
Phase 0 (baseline)	138.9±21.1	138.1±10.1	139.3±16.1	133.3±16.5	144.8±17.4	130.2±10.4
Phase I	134.3±19.0	137.4±15.1	144.4±17.1*	149.4±21.1**	140.5±21.1	130.6±16.4
Phase II	129.6±15.7	135.3±11.6	133.9±20.8	132.9±18.4	142.0±20.4	131.4±15.6
Phase III	134.0±18.1	134.4±13.0	139.5±15.1	142.4±21.2*	137.6±21.4	125.4±8.6

Means ± standard deviations of the data

*p = 0.021 – 0.040; **p = 0.001 – 0.02

Acronyms: AM= amlodipine; IB= ibuprofen; L/H= lisinopril/hydrochlorothiazide; PX= piroxicam.

FIG. 2 Percentual changes from baseline values in mean standing systolic blood pressure during the study periods



AM.IB= amlodipine±ibuprofen; AM.PX= amlodipine±piroxicam;

L/H.IB= lisinopril/hydrochlorothiazide±ibuprofen; L/H.PX= lisinopril/hydrochlorothiazide±piroxicam.

Error bars represent CI₉₅ of the calculated % differences.

Good blood pressure control (i.e. <140/90 mm Hg in the sitting position) was obtained in 68 of the 88 examinees (77.3%) at the inception of this trial. This high success rate was evenly distributed across the study arms, amounting at 76.9% among the control subjects, at 79.3% in the lisinopril/hydrochlorothiazide intervention subgroup (subsequently receiving either ibuprofen or piroxicam; n= 29), and at 75% in the amlodipine intervention subgroup (n= 20); the

observed between-group differences were insignificant ($\chi^2=0.130$; df 2; p= 0.937). The blood pressure control did not change appreciably during the formal study in the control ($\chi^2= 0.269$; df 3; p= 0.966) nor in the amlodipine interventional arm ($\chi^2=0.251$, df 3; p= 0.961), while in the lisinopril/hydrochlorothiazide arm it was markedly impaired by the addition of ibuprofen or piroxicam ($\chi^2=10.188$; df 3; p=0.017; phases I and III in Table 5).

TABLE 5 Blood pressure control during the trial

Period	Control group (n= 39)		L/H+NSAIDS group (n= 29)		AM+NSAIDS group (n= 20)	
	NT*	HT**	NT	HT	NT	HT
Phase 0 (baseline)	76.9%	23.1%	79.3%	20.7%	75.0%	25.0%
Phase I	74.4%	25.6%	44.8%	55.2%	70.0%	30.0%
Phase II	71.8%	28.2%	75.9%	24.1%	70.0%	30.0%
Phase III	74.4%	25.6%	51.7%	48.3%	75.0%	25.0%

*NT= normotensive, i.e. BP <140/90 mm Hg; **HT= hypertensive, i.e. BP \geq 140/90 mm Hg in the seated position
Acronyms: AM= amlodipine; L/H= lisinopril/hydrochlorothiazide

Body weight, contrary to the expectations, did not change significantly during this study (ANOVA: $F_{2,77}=1.813$; $p=0.159$). In the control group all the changes were within 0.3% limits ($p>0.870$), while in the intervention subgroups the average increase during the assumption of ibuprofen or piroxicam was 0.4 kg (0.45%; $p=0.230$), and the maximal increase was observed in phase I with piroxicam [from 79.6 ± 13.4 ($CI_{.95}=74.12-85.08$) to 81.4 ± 14.0 ($CI_{.95}=75.68-87.12$) kg; an average increase by 2.2%; $p=0.122$]. Side effects in this study were minor and expected; e.g., three patients in the amlodipine study group and five in the amlodipine control group complained of some ankle edema but none withdrew from the trial.

DISCUSSION

The present study was not sponsored, so we could only afford to give the drugs refunded by the Croatian Institute for Health Insurance. Over 95% of the prescriptions to the Croatian population are currently covered with this insurance, provided the prescribed drugs are on the “positive list”³⁰ (i.e., coxibs and some other NSAIDs were not enlisted). Among the available drugs, we chose the ones that are most prescribed, ibuprofen, acetaminophen and piroxicam. The design of the study was atypical since placebo could not be included because all the examinees had to take pain medications for severe osteoarthritic symptoms, and the control group (comparable hypertensives with no degenerative hip or knee disease) was included just to offer an insight into possible confounders, such as climatic or diet alterations. There are several limitations of this study, which also point to directions for future

research. First, it was not double blind but open with the prescriber physician unaware of the results, and the assessor physician unaware of the prescribed drugs (“one and a half blind”). It was also not placebo controlled (hardly acceptable on ethical grounds because of osteoarthritis severity). Second, we have not studied the global cardiovascular risk of these interactions (e.g. procoagulant or proinflammatory peculiarities) but just the impact on arterial pressure. Comparison with some recent studies or reviews²⁵⁻²⁸ may therefore be ill advised. Third, due to the number of suitable patients willing to participate (122 out of possible 223 or 54.7%; enrolled 88 or 39.5%), the relatively small sample size limits the power to prove possibly relevant differences between ibuprofen and piroxicam concerning blood pressure control (just a trend was shown indicating piroxicam as a more potent interactant), and a selection bias might impair the extrapolability of the results. However, in clinical terms, the distinction between piroxicam and ibuprofen in this sense is probably tenuous and insignificant.

Of course, this study has several advantages as well. It was performed in a busy family practice, highly resembling the real life circumstances in a transitional, post communist country. The factorial design with crossing-over of NSAID regimens enabled us to better delineate the role of individual agents. Since some authors describe acetaminophen as much less prone to the studied interaction^{4,13,29}, which others deny^{3,28}, we have included this drug as an “indifferent”, placebo-like agent during the wash-out interval between two “hard” NSAID periods. Acetaminophen distinctly ameliorated hypertension

control in this trial, showing remarkably little effect on blood pressure. However, only a placebo-controlled study could discern none from its slight, residual prohypertensive potential. In this respect, the distinction of acetaminophen from other COX inhibitors may be due to its peculiar mechanism of action.³¹

We have confirmed the prohypertensive activity of ibuprofen and piroxicam, known for decades.²⁻²⁹ On the other hand, the observed increase in blood pressure was much higher in our hypertensive examinees (some 8-12/6-8 mm Hg) than in general populations^{20,21} (some 3-4/1-2 mm Hg). This outstanding worsening of preexistent hypertension is clinically relevant, especially for elderly patients with polymorbidity, exposed to additional cardiovascular risk factors (e.g. diabetes, nephropathy).

Blood pressure control during this study was remarkably good, achieving normotension in over 75% of the examinees. The only exception was registered in the lisinopril/hydrochlorothiazide subgroups while receiving ibuprofen or piroxicam, when the therapeutic efficacy/effectiveness was almost halved! NSAID-induced increase in blood pressure is presumably dose-related, as shown with aspirin: low doses of 100 mg/day did not interfere with the control of hypertension^{10,12,19}, while doses of 300 mg/day did.^{11,19} Moreover, we have observed a downward trend in this adverse effect over time (phase I vs. phase III), which deserves further investigation since in a long run the interaction may become clinically less important.

Our data indicate that the fixed-dose lisinopril/hydrochlorothiazide combination, and by inference most diuretics and ACE inhibitors, lose a lot of their antihypertensive effect through an interaction with some NSAIDs, which is concordant with the majority of published trials^{3-12,14,16,17,19} but not all.¹³ On the other hand, amlodipine, and by inference most calcium channel blockers, be they dihydropyridines^{5,8,17,23,24} or nondihydropyridines⁹, resist this untoward interaction and are best suited for hypertensive patients taking concomitant NSAIDs.

Finally, since we have not observed a significant increase in body weight during the intake of the NSAIDs, it seems that the observed BP elevation was largely due to vasoconstriction and less so to volume expansion. Others^{8-10,16} have

reported significant weight gain implicating volume expansion. Radack et al.⁴ did not observe weight gain with ibuprofen nor with acetaminophen, while Klassen et al.⁸ reported a significant increase in body weight among 100 hypertensives treated with naproxen. These discrepancies deserve further study and clarification.

SUGGESTIONS

1. For most hypertensive patients with osteoarthritis or other conditions requiring chronic pain relief, particularly if at increased risk of hypertensive and/or atherosclerotic complications (e.g. elderly, diabetics, with impaired renal function), acetaminophen appears to be the safest treatment, while ibuprofen, piroxicam and some others (such as meloxicam and most coxibs) should be avoided.^{3-19,23-29}
2. The NSAIDs' prohypertensive effect, due more to vasoconstriction than to fluid retention, is much stronger in hypertensive than in normotensive subjects. It is seemingly dose dependent (as shown in other trials^{3,7,10,12,19}) and slightly fading over time.
3. Almost all antihypertensive drugs lose some of their efficacy when combined with NSAIDs. Calcium channel blockers are an exception, becoming drugs of choice for the subset of hypertensive population needing concomitant analgesic/anti-inflammatory treatment.

Acknowledgements

The authors are grateful to Žarko Bajić of Biometrika Healthcare Research, Zagreb, Croatia for skilful statistical help in planning this trial and in data evaluation.

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