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Renal-associated escape effect of antihypertensive therapy in hypertensive patients receiving nonsteroidal anti-inflammatory drugs ("PANDA" trial)

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Abstract

Objective. The subanalysis of the study "PANDA" (the study of renal function in patients with acute nonspecific pain in lower back during therapy with nonsteroidal anti-inflammatory drugs (NSAID)) is the study of renal-associated escape effect of antihypertensive therapy in patients with arterial hypertension (HTN) receiving NSAID. **Design and methods.** We included 407 patients receiving one of the following NSAIDs for 14 days: meloxicam (15 mg/day), etoricoxib (60 mg/day), nimesulide (200 mg/day) or celecoxib (200 mg/day). Five visits were performed. During the visits blood pressure (BP), glomerular filtration rate (GFR), blood levels of cystatin C were assessed. **Results.** At first step, all parameters were evaluated in the whole group (n = 407). As the second step, we analyzeds the indicators in 4 groups depending on the NSAID type. At the third stage (subanalysis) we allocated 3 groups of patients: 1 group (n = 62) — patients with a history of HTN and diabetes mellitus, group 2 (n = 173) patients with HTN, and group 3 (n = 172) — patients without HTN and diabetes mellitus. **Conclusions.** In patients with acute nonspecific back pain, with a history of HTN, NSAID intake is associated with the certain changes in BP, GFR and cystatin-C. Therefore, we can discuss a renal-associated escape effect of antihypertensive therapy. It is the most evident on the 7th day of NSAID therapy. All changes of the studied parameters should be considered as a class-effect adverse reactions of NSAIDs, without any benefits in relation to specific medications.

Key words: nonsteroidal anti-inflammatory drugs, glomerular filtration rate, cystatin C, arterial hypertension, blood pressure, decreased effectiveness of antihypertensive drugs

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Ренально-ассоциированный эффект «ускользания» антигипертензивной терапии у пациентов с артериальной гипертензией на фоне приема нестероидных противовоспалительных препаратов (результаты когортного исследования «ПАНДА»)

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Резюме

Цель исследования — субанализ исследования «ПАНДА» (изучение показателей функции почек у пациентов с острой неспецифической болью в нижней части спины на фоне терапии нестероидными противовоспалительными препаратами (НПВП)) — изучение ренально-ассоциированного эффекта «ускользания» антигипертензивной терапии у пациентов с артериальной гипертензией (АГ) на фоне приема НПВП. **Материалы и методы.** Включено 407 больных, получавших один из четырех НПВП: мелоксикам (в дозе 15 мг/сут), эторикоксиб (60 мг/сут), нимесулид (200 мг/сут) или целекоксиб (200 мг/сут) в течение 14 дней. На пяти визитах проводился контроль уровня артериального давления (АД), скорости клубочковой фильтрации (СКФ), показателей в крови цистатина С. **Результаты.** Анализ полученных результатов проводили поэтапно. На первом этапе все результаты оценивались во всей группе больных (n = 407). На втором этапе проводили анализ полученных показателей в 4 группах больных в зависимости от принимаемого НПВП. На третьем этапе (субанализ) нами были выделены 3 группы пациентов: 1-я группа (n = 62) — пациенты, в анамнезе у которых имелись АГ и сахарный диабет (СД), 2-я группа (n = 173) — пациенты с АГ и 3-я группа (n = 172) — пациенты без АГ и СД. **Выводы.** У больных с острой неспецифической болью в спине и АГ в анамнезе в период приема НПВП установлены статистически значимые закономерности изменения параметров систолического АД, диастолического АД, СКФ и цистатина С. Во взаимосвязи полученные данные позволяют говорить о ренально-ассоциированном эффекте «ускользания» антигипертензивной терапии, что особенно выражено на 7-й день приема НПВП. Все установленные изменения изучаемых показателей следует рассматривать как класс-эффект побочных реакций при приеме НПВП, без каких-либо преимуществ в отношении конкретного лекарственного средства.

Ключевые слова: нестероидные противовоспалительные препараты, скорость клубочковой фильтрации, цистатин С, артериальная гипертензия, артериальное давление, снижение эффективности антигипертензивных препаратов

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In real-world clinical practice nonsteroidal anti-inflammatory drugs (NSAIDs) are the most widely used treatment for acute and chronic pain. NSAIDs exert their main pain-relieving effect by blocking prostaglandins (PGs), the process that results from the inhibition of the cyclooxygenase (COX) enzyme [1]. In humans there are two COX isozymes: COX1 and COX2. The reaction of blocking COX and catalysis of arachidonic acid is a complex process because COX1 and COX2 are bifunctional enzymes influencing a whole cascade of peroxidase reactions with highly unstable intermediate reactions which occur spontaneously and involve endoperoxide and hydroperoxidase [2]. On the whole the amount of prostaglandins induced in a cell or tissue depends on the expression of COX1 and COX2. All NSAIDs are synthetic inhibitors of COX, but have various ways of interaction with and binding to the active pool of arachidonic acid; this predetermines their pharmacological specificity in terms of side effects [3]. It is known that the blocking of the COX-PG system though several mechanisms, among them those involving renal macrophages and T-cell infiltration, is related to the onset of hypertension [4].

The clinical efficacy of NSAIDs and the range of their side effects are regarded in terms of the priority of action towards a particular COX isozyme. However, COX specificity is only one of the factors determining a NSAID safety profile. Most NSAIDs inhibit both isozymes, and besides some differences related to COX1 and COX2 specificity, product characteristics depend on drug interaction pharmacodynamics, patient characteristics and the patient's physical status. Clinical research physicians have now focused on the NSAID side effects as these have become very common, especially among patients who have a history of vascular diseases (including hypertension), diabetes mellitus, chronic kidney disease, and gastrointestinal diseases. The most common adverse events related to NSAIDs are peptic ulcer disease, acute kidney injury, increased risk of a stroke and a heart attack [5–9]. Such a wide range of potential adverse events can be explained by a number of factors including oxidative stress in healthy organs and tissues [6–11]. These class effects should be taken into consideration when NSAIDs are prescribed to different categories of patients depending on their physical status and potential risks of adverse events. In clinical practice basic guidelines have been established for patients who have had myocardial infarction, heart failure, hypertension and other cardiovascular events, and practitioners are instructed to prescribe NSAIDs in the minimum effective dose and for a minimum period of time [12].

At present, the results of a whole series of studies of NSAID-related side effects have been extremely contradictory. Nevertheless, this class of drugs is most actively used in real-world conditions to manage pain in patients of different gender, with various demographic and clinical characteristics. As the study by Fosbol EL et al. (2009) has shown, the risks of cardiovascular complications during treatment with NSAIDs are high even among individuals who are considered healthy [13]. Taking this into account, nowadays it is essential to study some sides of the issue, including the influence of NSAIDs on the changes in blood pressure parameters in patients with hypertension, as this will allow more elaborate strategies of safer dosing regimens in different groups of patients. It is particularly important to investigate those NSAID side effects that are related to drug interaction, especially with antihypertensive drugs in patients with a history of hypertention; special focus should be given to conditions that precede such negative combinations [14].

Within the PANDA cohort study (the study of renal function indicators in patients with acute nonspecific low back pain receiving therapy with nonsteroidal anti-inflammatory drugs) we have conducted a subanalysis aimed at studying renal associated "escape" of antihypertensive therapy in patients with hypertention receiving NSAIDs.

Materials and Methodology

General subject characteristics

The clinical model of this study implied enrolment of patients with acute nonspecific low back pain requiring treatment with NSAIDs. The study enrolled 407 patients (189 male and 218 female subjects constituting 46.4% and 53.6% of the study population, respectively), with the mean age of 56.59 ± 6.87 years. The following inclusion criteria

were applied to patients in the PANDA study: 1) age from 45 to 70 years, inclusive, regardless of gender; 2) the patient presents to an outpatient clinic with low back pain for the first time during the calendar year; 3) the patient has not been treated with NSAIDs during the previous 3 months; 4) no instances of hypertensive crisis have occurred during the previous 4 weeks, as objectively documented in the automated information system "Polyklinika"; 5) in case of patients with a history of hypertention: the patient should be committed to antihypertensive therapy (according to outpatient medical records). The following exclusion criteria were applied: 1) verified (documented) chronic kidney disease; 2) earlier instance of a stroke and/or transient ischemic attack; 3) erosion or ulceration in the mucous membrane of the stomach or duodenum; 4) acute gastrointestinal hemorrhage; 5) cerebrovascular or other hemorrhage; 6) exacerbation of an inflammatory bowel disease (Crohn's disease, indeterminate ulcerative colitis); 7) hemophilia or other coagulation defects; 8) evident symptoms of heart failure: cardiac function corresponding to class II–IV (chronic heart failure) according to the classification of New York Heart Association (NYHA); 9) severe hepatic failure [Child–Pugh score of more than 9] or active liver disease; 10) period following coronary artery bypass surgery; 11) clinical signs of ischemic heart disease; 12) signs of specific injury to spine, as well as nerve root compression syndrome.

Study design

This multicenter prospective study was conducted on the base of eight city outpatient clinics in Samara, Russia, from 12 April 2016 to 25 September 2016. A total of 1015 patients were screened, and 407 of them met the inclusion criteria and received treatment with NSAIDs. The subjects were randomized into four groups using the envelope method. Patients received meloxicam (15 mg/day) in group I (n = 103), etoricoxib (60 mg/day) in group II (n = 103), nimesulide (200 mg/day) in group III (n = 101), and celecoxib (200 mg/day) in group IV (n = 100). The patients were monitored for 21 days, with five visits (V) conducted during that period: four visits (V_1-V_4) were held during treatment with NSAIDs and the fifth visit (V_5) took place in the follow-up period. According to the protocol, the timing of visits was the following: V_1 occurred when the patient initially presented to the medical institution and started treatment with a NSAID; V_2, V_3, V_4, V_5 were held after 3, 7, 14 and 21 days, respectively. It should be noted that no analgesic, muscle relaxant or anticonvulsant drugs were used in order to avoid drug interaction that would mingle with NSAID side effects. Prior to NSAID prescription at V_1 the patients were given detailed and consistent explanation of the study design and were informed of all possible side effects of NSAIDs; the patients also gave written consent for the processing of their personal data and for study participation. All patients were informed that they had the right to leave the study at any moment for any reason.

At the first visit (prior to drug prescription) and all the following visits pain intensity was assessed using the visual analogue scale (VAS) (in centimetres) and office BP was measured using a double-checked auscultatory semi-automatic sphygmomanometer with readings performed at 12 minute intervals (mean BP value was calculated). Blood chemistry was tested using the automated Sapphire 400 Biochemistry Analyzer (by Hirose Electronic System, Japan) and included the following parameters: glucose, creatinine, total cholesterol, low-density lipoproteins (LDLs), and triglycerides. Glomerular filtration rate (GFR) was calculated using the CKD-EPI formula [15]. Cystatin C in serum was measured in an immunoturbidimetric test (the calibrator meets the European Reference Material standard ERM-DA471/IFCC) using the DiaSys diagnostic kit (Germany).

The results were analyzed in stages. During stage 1 the results were assessed for the whole number of patients (n = 407). At stage 2 the obtained parameters were evaluated for four groups of patients depending on the prescribed NSAID. During stage 3 (subanalysis) patients were allocated to three groups: group I (n = 62) included patients with a history of hypertension and diabetes; group II (n = 173) included patients with hypertension; and group III (n = 172) included patients without hypertension or diabetes.

The statistical analysis of data was performed using the IBM SPSS Statistics 21 software (licence no. 201306263). One-way analysis of variance (ANOVA) was carried out to compare independent groups. If the null hypothesis of equal means for groups was rejected, post-hoc analysis was conducted (pairwise comparisons) according to Tukey's method. To compare parameter dynamics ANOVA with repeated measures was used. Relationships between values were assessed using Pearson's correlation.

The description of normally distributed quantitative values is represented by the mean value and mean square deviation (standard deviation) (M ± SD). To perform the analysis we used descriptive statistics with a parametric test (Student's *t*-test). Nonnormal data were represented by the median, the upper quartile (25th quartile) and lower quartile (75th quartile) values — Me [Q25; Q75]. The differences between values were considered statistically significant in case of $p < 0.05$.

The study was conducted in compliance with Good Clinical Practice (GCP) and the principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Samara State Medical University.

Results

All patients finished their participation in the study without protocol violations. The mean duration of treatment with NSAIDs was 13.36 ± 1.02 days. In the whole group of patients pain was managed successfully and was evaluated at 2.33 ± 1.8 cm according to VAS by the end of the NSAID treatment. No NSAID-related adverse events were reported to the Federal Authority for Healthcare Regulation of the Russian Federation.

During stage 1 of the study the results were assessed for the whole number of patients (n=407), whose general clinical characteristics at baseline are presented in Table 1. Pain was rated at 6.78 ± 1.22 cm according to VAS, which indicated high pain intensity among the study subjects and constituted a sufficient indication for treatment with NSAIDs. Out of all study patients 173 (42.5%) subjects had a history of hypertension supported by medical records, 62 (15.2%) patients had a registered type 2 diabetes as well as a history of hypertension. These conditions were compensated in all patients, and the subjects were committed to therapy with antihypertensive and hypoglycemic drugs. At the beginning of the study the mean values of all laboratory parameters were within the reference range. In accordance with the European Guidelines on Hypertension Management (2013), the office BP value was stratified as high normal BP [16].

Table 2 shows the measurement dynamics for all enrolled patients and includes such parameters as systolic blood pressure (SBP), diastolic blood pressure (DBP), GFR and cystatin C levels during treatment with NSAIDs and subsequently (on Day 21 of the study). Changes in BP indicated the following trend: a statistically significant elevation of SBP and DBP occurred on Days 3 and 7 followed by a decrease and return to normal values at V_4 and V_5. There was no statistically significant difference between the baseline SBP/DBP and the values obtained on Days 14 and 21 of the study. According to the collected data, the GFR parameter decreased by V_2 with a statistically significant drop recorded in the period from V_1 to V_3 followed by

Table 1

GENERAL PATIENT CHARACTERISTICS IN ALL GROUPS AT BASELINE (n = 407)

Parameter	Patients (n = 407)	
	M ± SD	Me [Q25; Q75]
BMI, kg/m^2	27.56 ± 4.32	29.00 [26.00;31.00]
TC, mmol/L	4.5 ± 1.19	4.81 [4.32; 5.62]
LDL C, mmol/L	2.4 ± 0.89	2.75 [2.14; 3.05]
TG, mmol/L	1.17 ± 0.53	1.33 [1.11; 2.26]
Glucose, mmol/L	5.3 ± 1.3	5.70 [4.90; 6.50]
GFR calculated using CKD EPI, mL/min/1.73m^2	89.37 ± 9.22	89.00 [82.00; 98.00]
Cystatin C, mg/L	0.64 ± 0.11	0.62 [0.55; 0.69]
SBP, mmHg	137.26 ± 9.12	139.00 [129.00; 140.00]
DBP, mmHg	74.84 ± 7.13	75.00 [69.00; 81.00]

Note: The data are presented as mean values and standard deviation (M±SD) or as median and interquartile range — Me (25th and 75th percentiles). Abbreviations in Tables 1–4: VAS — visual analogue scale, DBP — diastolic blood pressure, BMI — body mass index, LDL C — low-density lipoprotein cholesterol, SBP — systolic blood pressure, GFR — glomerular filtration rate, TG — triglyceride, TC — total cholesterol, CKD-EPI — the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

Table 2

PARAMETER DYNAMICS IN ALL GROUPS OF PATIENTS (n = 407)

Parameters	Visits and Statistical Significance of Differing Values								
	V_1	V_2	V_3	V_4	V_5	p_{ANOVA}	p_{1-5}	p_{1-3}	p_{3-5}
GFR calculated using CKD EPI, mL/min/1.73m^2	89.37 ± 9.22	88.66 ± 9.54	84.66 ± 11.90	85.20 ± 11.65	89.21 ± 9.92	< 0.001	0.999	0.000	0.000
Cystatin C in blood, mg/L	0.64 ± 0.11	0.81 ± 0.21	0.83 ± 0.24	0.67 ± 0.15	0.67 ± 0.14		0.678		
SBP, mmHg	137.26 ± 9.12	138.88 ± 10.25	140.55 ± 11.17	135.83 ± 8.26	136.05 ± 8.39		0.724		
DBP, mmHg	74.84 ± 7.13	77.26 ± 8.45	80.34 ± 10.69	74.39 ± 6.66	74.47 ± 6.71		0.999		

Note: The data are presented as mean values and standard deviation (M ± SD).

an increase by V_4 and V_5. There was no statistically significant difference between the baseline GFR and the values obtained on Day 21. A statistically significant increase in cystatin C was recorded after three days of therapy reaching its peak by V_3 and then decreasing by V_4. At the end of the study there was no statistically significant difference in values collected from V_1 to V_5. It should be noted that the whole-group mean GFR and cystatin C levels were within the reference range.

Thus, the first stage analysis of the whole-group data showed that, despite the observed changes, there were no clinically significant negative tendencies indicating the impairment of renal function, as shown by the statistical analysis of data from all groups of patients with acute back pain taking NSAIDs. The correlation analysis revealed statistically significant correlation between the elevated SBP ($r = 0.441$; $p = 0.000$)/DBP ($r = 0.449$; $p = 0.000$) and the increased level of cystatin C as well as decreased GFR: SBP ($r = –0.503$; $p = 0.018$), DBP ($r = –0.499$; $p = 0.007$) at V_3.

Further during stage 2 the pairwise comparisons test (Table 3 and Figures 1 and 2) showed no statistically significant difference in values compared at all five visits for patients randomized into groups according to the prescribed NSAID. The changes in GFR, cystatin C, SBP and DBP had an equal confidence level in the data of patients receiving meloxicam, etoricoxib, nimesulide and celecoxib. Figures 1 and 2 clearly demonstrate that SBP and DBP tended to rise in all four groups starting from Day 3 and reached a peak by V_3. Afterward BP decreased returning to baseline value by V_4 and remained stable during the period without the NSAID therapy.

Therefore, in general the results of stage 2 revealed BP elevation in the period from V_2 to V_3 followed by a return to baseline values. Should any group of patients be regarded only as individuals of certain age and gender who are receiving NSAIDs for pain management, it can be presupposed that this class of drugs raises BP irrespective of drug selectivity, but this increase is not clinically significant. The changes in the GFR and cystatin C parameters correlate with the elevation of SBP and DBP, and this correlation is statistically significant.

A striking difference emerged in the results of stage 3 analysis which included patients with hypertension, or hypertension and diabetes at baseline. Group III included the youngest population

Table 3

DYNAMICS OF BP, GFR, AND CYSTATIN C AT VISITS V_1-V_5

Визиты	Мелоксикам	Эторикоксиб		Нимесулид	Целекоксиб	p_{ANOVA}
	SBP, mmHg					
V_1	136.91 ± 8.33	136.56 ± 9.46		137.45 ± 9.32	138.14 ± 9.38	0.633
V_2	139.30 ± 9.73	138.19 ± 10.72		138.81 ± 10.29	139.23 ± 10.35	0.861
V_3	140.81 ± 10.48	140.13 ± 11.63		140.90 ± 11.85	140.35 ± 10.78	0.954
V_4	135.58 ± 7.56	135.29 ± 8.58		136.08 ± 8.39	136.39 ± 8.56	0.783
V_5	136.06 ± 7.93	135.44 ± 8.64		136.22 ± 8.45	136.50 ± 8.62	0.832
	DBP, mmHg					
V_1	74.79 ± 7.09	74.60 ± 7.18		75.00 ± 7.43	74.96 ± 6.91	0.978
V_2	77.53 ± 8.23	77.08 ± 8.91		77.18 ± 8.44	77.23 ± 8.33	0.983
V_3	80.75 ± 10.57	80.04 ± 10.67		80.48 ± 10.93	80.10 ± 10.74	0.961
V_4	74.20 ± 6.34	74.09 ± 6.80		74.66 ± 7.12	74.62 ± 6.44	0.901
V_5	74.19 ± 6.38	74.17 ± 6.77		74.72 ± 7.14	74.82 ± 6.63	0.853
	GFR, mL/min/1.73m^2					
V_1	89.69 ± 9.30	89.17 ± 9.34		89.30 ± 9.28	89.33 ± 9.09	0.981
V_2	88.84 ± 9.50	88.60 ± 9.60		88.45 ± 9.79	88.73 ± 9.39	0.992
V_3	84.74 ± 12.01	84.43 ± 12.00		84.61 ± 12.10	84.86 ± 11.65	0.995
V_4	84.86 ± 11.98	85.50 ± 11.69		85.14 ± 11.66	85.30 ± 11.44	0.983
V_5	89.26 ± 10.03	88.95 ± 9.89		89.60 ± 9.63	89.01 ± 10.24	0.965
	Cystatin C, mg/L					
V_1	0.64 ± 0.11	0.65 ± 0.11		0.64 ± 0.11	0.64 ± 0.12	0.908
V_2	0.81 ± 0.22	0.80 ± 0.20		0.81 ± 0.19	0.81 ± 0.21	0.987
V_3	0.84 ± 0.25	0.84 ± 0.24		0.82 ± 0.24	0.84 ± 0.25	0.977
V_4	0.68 ± 0.17	0.68 ± 0.16		0.67 ± 0.14	0.66 ± 0.15	0.842
V_5	0.67 ± 0.14	0.67 ± 0.14		0.67 ± 0.13	0.66 ± 0.14	0.976

Note: The data are presented as mean values and standard deviation (M ± SD).

with mean age of 50.43 ± 3.27 years; in group II mean age was 59.62 ± 4.39 years, and in group I it was 64.97 ± 5.12 years. All patients with a history of hypertension received antihypertensive drugs. In group I combination therapy was given to 39 (62.9%) patients and included angiotensin-converting-enzyme inhibitors (ACE inhibitors) and/or angiotensin II receptor blockers (ARBs) and diuretics. Monotherapy with ACE inhibitors or ARBs was given to 23 (37.1%) subjects in group I. In group II 98 (56%) subjects were constantly undergoing monotherapy with antihypertensive agents (either ACE inhibitors or ARBs or diuretics) and 75 (43.4%) patients were taking combination drugs.

Table 4 and Fig. 3–6 show the changes in SBP, DBP, cystatin C and GFR compared throughout all visits as well as confidence levels of changes at $V_{4–5}$ and $V_{1–5}$. Period $V_{4–5}$ is essential to understand how a drug affects the described parameters, as according to the study protocol, starting from Day 14 treatment with NSAIDs was stopped for all patients. The data collected in period $V_{1–5}$ allowed the comparison of baseline values with the end-of-study results.

There was a statistically significant elevation of SBP and DBP in groups I and II starting from V2, followed by return to baseline levels at V4. Thus, from the third day of the NSAID therapy the escape phenomenon of antihypertensive therapy emerged, despite earlier sufficiency of treatment in controlling hypertension. In patients without hypertension BP remained almost without changes. There was also a statistically significant increase in the level of cystatin C in the period until V3 with return to normal values by the end of the NSAID therapy. The de-

Figure 1. Systolic blood pressure dynamics in patients during the period from V_1 to V_5

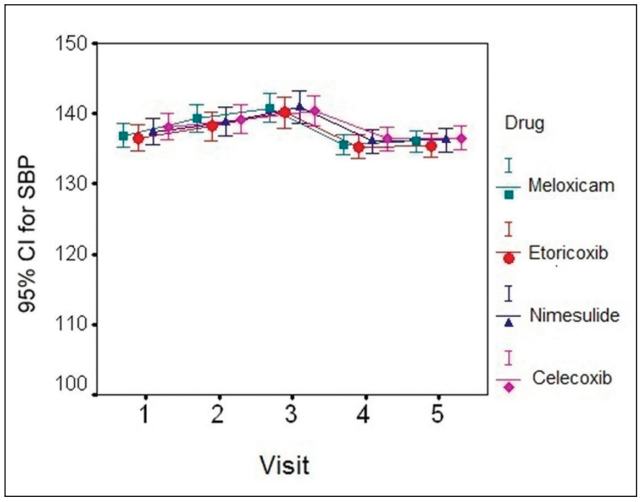

Figure 2. Diastolic blood pressure dynamics in patients during the period from V_1 to V_5

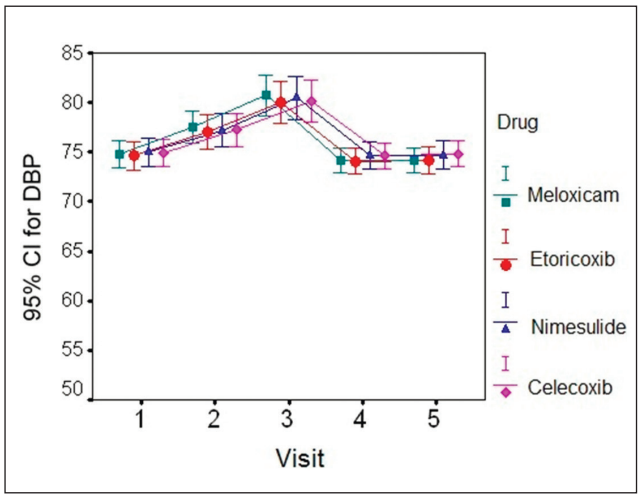

Figure 3. Systolic blood pressure dynamics in patients with and without hypertension during the period from V_1 to V_5

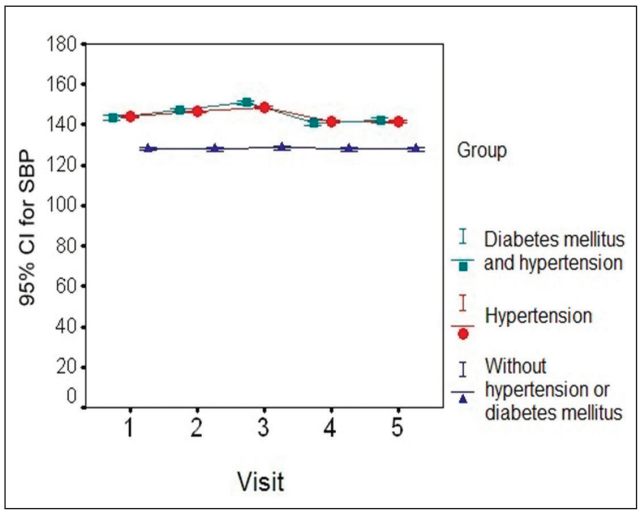

Figure 4. Diastolic blood pressure dynamics in patients with and without hypertension during the period V_1 to V_5

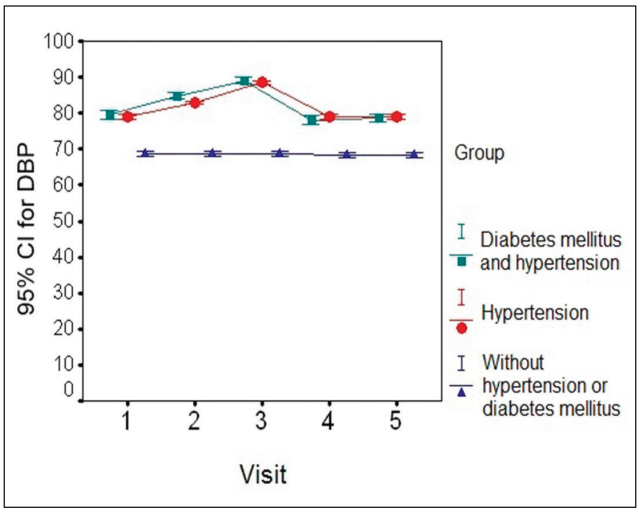

Figure 5. Cystatin C dynamics in patients with and without hypertension during the period from V_1 to V_5

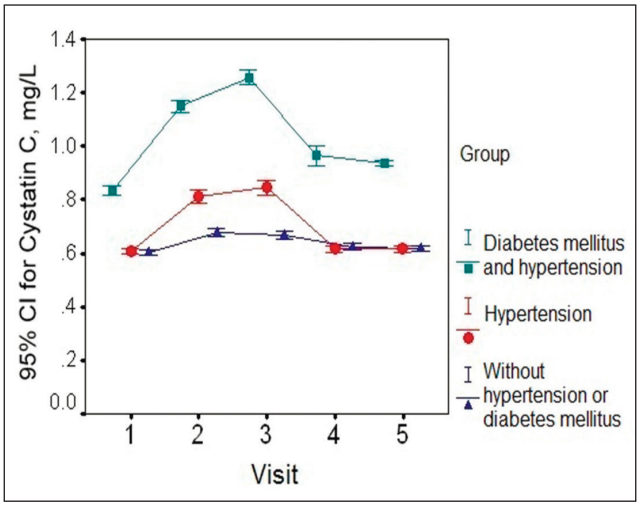

Figure 6. Glomerular filtration rate dynamics in patients with and without hypertension during the period from V_1 to V_5

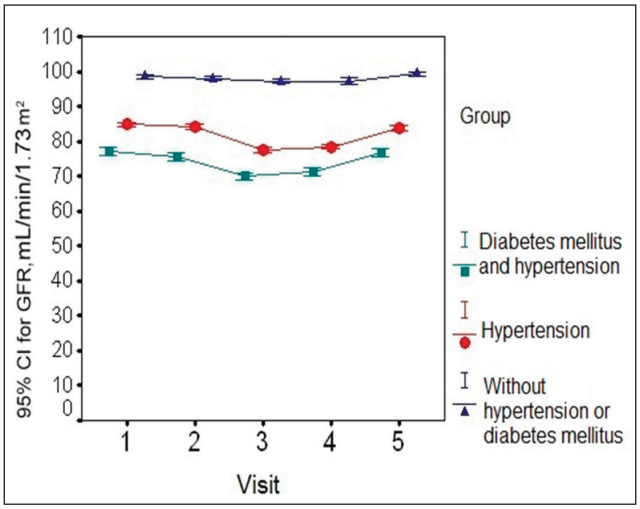

Table 4

DYNAMICS OF SBP, DBP, GFR, AND CYSTATIN C COMPARED BETWEEN GROUPS OF PATIENTS WITH AND WITHOUT HYPERTENSION

Parameters	Visits					p	
	V_1	V_2	V_3	V_4	V_5	p_{4-5}	p_{1-5}
Group I (n= 62)							
SBP, mmHg	143.61 ± 4.96	147.31 ± 2.58*	150.87 ± 2.89*	140.95 ± 5.01*	142.39 ± 4.81	0.315	0.480
DBP, mmHg	79.60 ± 4.90	84.74 ± 3.46*	89.08 ± 3.88*	78.10 ± 4.33*	78.65 ± 4.38	0.951	0.718
GFR calculated using CKD EPI, mL/min/1.73m^2	77.21 ± 4.77	75.52 ± 4.64*	70.02 ± 3.80*	71.23 ± 4.52	76.58 ± 4.71*	0.001	0.937
Cystatin C, mg/L	0.83 ± 0.07	1.15 ± 0.09*	1.26 ± 0.11*	0.96 ± 0.14*	0.94 ± 0.04	0.576	0.001
Group II (n= 173)							
SBP, mmHg	143.84± 4.31	146.43 ± 3.06*	148.48 ± 3.62*	142.63 ± 4.04*	141.72± 4.17	0.089	0.999
DBP, mmHg	79.14 ± 4.66	82.89 ± 3.27*	88.49 ± 3.45*	78.12 ± 3.41*	78.93 ± 4.17	1.000	0.986
GFR calculated using CKD EPI, mL/min/1.73m^2	84.84 ± 4.27	84.18 ± 4.44*	77.67 ± 5.43*	78.44 ± 4.91	83.93± 5.32*	0.001	0.412
Cystatin C, mg/L	0.61 ± 0.08	0.81 ± 0.17*	0.85 ± 0.18*	0.62 ± 0.08*	0.62 ± 0.08	1.000	0.975
Group III (n=172)							
SBP, mmHg	128.16 ± 5.37	128.04 ± 6.08	128.61 ± 5.95	128.03 ± 4.41	127.90 ± 5.30	0.993	1.000
DBP, mmHg	68.66 ± 5.04	68.73 ± 5.45	68.71 ± 5.05	68.55 ± 4.02	68.37 ± 4.37	1.000	0.981
GFR calculated using CKD EPI, mL/min/1.73m^2	98.48 ± 4.28	98.06 ± 4.18	97.19 ± 4.18	97.26 ± 5.36	99.24± 3.24*	0.001	0.473
Cystatin C, mg/L	0.60 ± 0.07	0.68 ± 0.09	0.67 ± 0.09	0.62 ± 0.08*	0.62 ± 0.07	0.949	0.373

Note: The data are presented as mean values and standard deviation (M ± SD).

crease in GFR persisted for a longer period than changes in BP and cystatin C, and it was precisely until the end of therapy that GFR remained low in groups I and II, and increased only by V5. The correlation analysis showed statistically significant correlation between the increase in BP and the changes in renal function indicators which became most evident at V3. It was exactly by Day 7 of the NSAID treatment that patients with hypertension required dose correction for their antihypertensive therapy. For example, the following statistically significant correlations were discovered in group I at V3: elevated SBP correlated with a higher level of cystatin C (r = 0.068; p = 0.0018), elevated SBP correlated with decreased GFR (r = –0.064; p = 0.0033), as well as elevated DBP correlated with a higher level of cystatin C (r = 0.059; p = 0.0081), and the elevated DBP correlated with decreased GFR (r = –0.065; p = 0.0045). The following statis-tically significant correlations were discovered in group II at V3: elevated SBP correlated with a higher level of cystatin C (r=0.054; p = 0.0027), elevated SBP correlated with decreased GFR (r= –0.059; p = 0.0054), as well as elevated DBP correlated with a higher level of cystatin C (r = 0.061; p = 0.0072), and the elevated DBP correlated with decreased GFR (r = –0.063; p = 0.0088).

An important outcome of stage 3 of the study was that the absence of changes in BP, GFR and cystatin C among patients without hypertension produced a favorable statistical effect in the group in general and created an illusion that there was no clinically significant influence of NSAIDs on the whole group of patients. In fact, for patients with hypertension there were some statistically significant changes in BP and they correlated with changes in renal function parameters with a high confidence level.

Discussion

The subanalysis within the PANDA study was conducted to explore the possibility of a renal associated escape of antihypertensive therapy in patients with hypertension receiving NSAIDs. The reason for conducting this study was the lack of consensus on the safety of NSAIDs when prescribed as a short-term therapy for this category of patients. The elevation of BP is typical of all NSAIDs, and this characteristic is listed in patient information leaflets for these drugs. Some fundamental studies conducted more than 30 years ago defined the role of mediated inhibition of PGs as an underlying mechanism which causes hyperkalemia, hyponatremia, and metabolic acidosis with increased water absorption in distal renal tubules, accompanied by BP elevation and by the edema syndrome [16–19]. PGs are vital mediators playing a crucial role in the regulation mechanisms of renal hemodynamics. Through the system of thromboxane A2 (TXA2) and prostacyclin (PGI2) PGs maintain the balance between hypertension and hypotension mechanisms in the body [20–22]. In case of hypertension (which mostly implies the activity of the sympathetic nervous system and renin–angiotensin–aldosterone system), NSAIDs given as treatment block COX, which leads to inhibited PG synthesis. As a result, vasoconstriction reactions prevail, followed by BP elevation [23].

We were based on the assumption that patients with hypertension were taking antihypertensive drugs to reach the desired BP readings, and this was true both in the whole group of patients and in the group of subjects with hypertension at baseline. However, the fact of such a significant elevation of BP in groups of patients with hypertension taking NSAIDs demonstrates the escape of antihypertensive therapy. Adverse drug interactions are the key issues in clinical pharmacology. For instance, Gavrilescu CM et al. (2016) assessed drug side effects in terms of cardiovascular risks on the basis of 81 cases of drug-induced hypertension, including 43 patients with hypertensive crises. The authors conclude that some drugs, including NSAIDs, can act on the same patient by multiple pathogenic links causing adverse reactions that persist in time [24]. The problem of drug interaction between NSAIDs and antihypertensive drugs means that control over hypertension is lost. The key factor of this adverse reaction is PG inhibition on the one hand and the impact on renin–angiotensin–aldosterone system [25–26] on the other. The known phenomenon when COX-2 inhibition leads to the development and aggravation of hypertension is mainly explained by renal sodium retention caused by COX2 inhibition [27, 28]. The use of COX2selective inhibitors is related to the increase of cardiovascular mortality risks; these include BP elevation as well as sodium and water retention that combine with accelerated thrombogenesis [29, 30]. The degree to which COX exhibition affects PGs is determined by genetic predisposition. The above data were published following experimental studies conducted by Facemire CS et al. (2010), researching the impact made on microsomal prostaglandin e synthase 1 (mPGES 1), the inhibition of which leads to hypertension in mice [31].

The present study has revealed negative tendencies with statistically significant correlation found between the elevation of SBP, DBP and changes in GFR and cystatin C in the group of patients with hypertension. The short-term treatment with a NSAID in particular not only became a significant factor causing the actual BP elevation, but also brought on the changes in renal function indicators. Apparently, when COX inhibition occurs, PGs lose their capacity to regulate BP and to support its renal adaptive regulation mechanisms.

Conclusions

The subanalysis conducted within the PANDA study resulted in the following conclusions. Among patients with a history of hypertension who had acute nonspecific back pain and received NSAIDs statistically significant trends were discovered in the changes of SBP, DBP, GFR and cystatin C parameters. In correlation the obtained data enable us to report the existence of a renal associated escape of antihypertensive therapy which becomes most evident on the seventh day of the NSAID therapy. A need exists to correct antihypertensive therapy and personalize the hypertension-related treatment if NSAIDs are prescribed for managing acute back pain in patients whose treatment regimen for hypertension includes ACE inhibitors, ARBs and diuretics. All the changes in the discussed parameters should be viewed as class-effect adverse reactions related to NSAIDs, with no advantages for any particular drug.

This was a pilot study conducted to investigate the use of NSAIDs by patients with hypertension, and there is a demand for further research of NSAID effects in the treatment of this group of patients.

Disclosable Financial Interests and Arrangements

All the listed authors have authority over concept development and preparation of this manuscript. There was no sponsorship for the present study. The study was not aimed at assessing clinical advantages of any particular drug. In case of dispute the authors will be ready to provide the study protocol as well as all source documents pertaining to the study. The authors bear full responsibility for submitting the final version of the manuscript for publication.

Conflict of interest

The authors declare no conflict of interest.

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