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ORIGINAL ARTICLE

Correlation of Body Mass Index and Orthostatic Hypotension in Patients with Hypertension on ACE Inhibitor Monotherapy

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Abstract

Background/Aim: Orthostatic hypotension (OH) is considered to be a drop in the systolic and diastolic blood pressure (> 20 mmHg; > 10 mmHg) 3 minutes from postural changes. The objective of this study was to analyse the correlation of body mass index (BMI) and OH during the treatment with trandolapril, as a single-drug treatment of hypertension.
Methods: The study involved 255 patients (average age 54.3 ± 11.7; 54.1 % men) with poorly regulated hypertension, who were given trandolapril as a single-drug treatment. The patients were divided into two groups regarding stage of hypertension: first-degree arterial hypertension (140-149 mmHg for systolic and 90-109 mmHg for diastolic blood pressure) and second-degree arterial hypertension (> 150 for systolic and > 110 mmHg for diastolic blood pressure). Incidence of OH occurrence was then analysed regarding hypertension stage and BMI during 6 months of follow-up, on 4 control examinations.
Results: During 24-week period after trandolapril introduction into the treatment of hypertension, a statistically significant difference in systolic, diastolic and mean blood pressure values was observed. No statistically significant difference was observed in incidence of OH between the first and second as well as between third and fourth examination during the study. Regarding the incidence of OH in normal body weight and obese patients, there was also no statistically significant difference.
Conclusion: As shown in this study, trandolapril, along with some other ACE inhibitors, has shown good balance in hypertension control and OH occurrence.

Key words: Orthostatic hypotension; Trandolapril; Body mass index.

Introduction

Angiotensin converting enzyme (ACE) inhibitors are commonly used antihypertensive drugs, not just for hypertension, but also for various cardiovascular diseases.[1] The mechanism of action disables angiotensin I to angiotensin II conversion, all by blocking the ACE, which consequently decreases angiotensin II activity. Moreover, ACE inhibitors lower catecholamine activity and interfere in vascular remodelling,[2] which enables its widespread use.

Trandolapril is a non-sulfhydryl-containing type of ACE inhibitor. Affinity of binding trandolaprilat to the ACE is very high. Compared to other ACE inhibitors, required dose for blocking 50 % of ACE is similar to ramiprilat.[3] Blood pressure (BP) values

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change depending on the body position. Usually a discreet drop of systolic and a discreet increase of diastolic blood pressure (DBP) occur when rising into standing position from a horizontal one. Orthostatic hypotension (OH) occurs when these changes are greater: for systolic blood pressure (SBP) a drop more than 20 mmHg and for DBP drop more than 10 mmHg within 3 minutes from the postural changes.[4] It can occur no matter of age or sex. The OH prevalence increases with age, estimated at 5-30 % in population over 65 years of age.[5] It can present with a range of unpleasant symptoms such as dizziness, nausea, headache, weakness, palpitations, etc. Therefore, it is recommended to gradually introduce the hypertension treatment and to measure blood pressure in lying or sitting / standing position once in a while, especially in patients older than 50, in order to prevent OH and its symptoms.[6] By its aetiology, OH can be neurogenic or non-neurogenic, while in terms of symptoms onset it can be initial, classic or delayed. Some antihypertensive drugs are associated with OH as their side effect.[7] Patients suffering from essential hypertension can have various and individual response to different antihypertensive drugs. Therefore, it is necessary to examine and determine patients' response to ACE inhibitors, in order to estimate risk and occurrence of OH.[21] The selection of adequate antihypertensive drug for different patients must be done thoroughly, taking into consideration incidence of OH in certain groups of patients.

The objective of this study was to analyse the correlation of body mass index (BMI) and OH during the treatment with trandolapril, generic representative of the ACE inhibitors, as a single-drug therapy.

Methods

This prospective study involved 255 patients with poorly regulated arterial hypertension. To these patients, trandolapril was introduced as a monotherapy. Follow-up period was 24 weeks.

Poorly regulated arterial hypertension was defined as SBP greater than 140 mmHg and for DBP greater than 90 mmHg measured two times in separate examinations. Patients were distributed in two examination groups, considering values of BP. The first group included patients with first-degree arterial hypertension (SBP between 140-149 mmHg, DBP between 90-109 mmHg) and the second group considered patients with second-degree arterial hypertension (SBP ≥ 150 mmHg and DBP ≥ 110 mmHg). Excluding criteria were as follows: patients younger than 18, pregnancy (positive β-hCG test), nursing mothers, patients with OH, patients with renal failure stage II or greater, patients with microalbuminuria > 300 mg / 24 h, patients with electrolytic disbalance, cardiac arrhythmias, anaemia (haemoglobin levels < 100 g/L), liver enzymes ≥ 1.5 times greater than reference values.

At the beginning of the study, every patient underwent physical examination, body weight and height measurement, BMI was calculated, 12-lead ECG was performed with heart rate calculation. BP was measured at every examination in sitting and standing position. Measurements were performed using mercury sphygmomanometer with cuff placed to cover two thirds of upper arm surface and minimum 80 % of upper arm circumference. BP was measured consecutively three times at each arm, with one-minute breaks between the measurements and mean values were calculated afterwards. Control visits were performed at 6th, 12th and 24th week after inclusion to the study. At each visit, doses of trandolapril were corrected in order to achieve adequate BP control (≤ 120/80 mmHg). Prior the inclusion, every patient had signed informed consent for participation. The research has been granted by the Ethics Committee of the Dedinje Cardiovascular Institute in Belgrade.

Statistical analysis was performed using descriptive statistical methods and analysed in ANOVA repeated measurements. IBM SPSS 18.0 software was used.

Results

The study included 255 patients, 138 men (54.1 %) and 117 women (45.9 %), average age 54.3 ± 11.67 years (Figure 1). The average BMI value was 27.73 ± 4.7, ranging from 17.3 to 36.6. According to BMI values, 2 (0.8 %) patients were underweight (BMI < 18.5), 35.3 % had normal weight (BMI between 18.5 and 25) while 163 (63.9 %) patients were overweight (BMI > 25). In the first study group, 127 (49.8 %) patients had first-degree hypertension, while 128 patients (50.2 %) had the second-degree hypertension.

Table 1: Blood pressure values of hypertensive patients on monotherapy with trandolapril

Haemodynamic parameters (X±SD)	Measurement period				Significance #
	Prior to therapy	After 4-6 weeks	After 12-14 weeks	After 24-26 weeks	
Systolic pressure	152.60 ±11.03	141.33 ±15.41	132.93 ±10.48	127.11 ±6.05	p=0.000*
Diastolic pressure	90.60 ±8.43	85.03 ±7.52	81.35 ±6.36	78.87 ±5.20	p=0.000*
Mean arterial pressure	110.80 ±10.02	103.78 ±8.58	98.91 ±7.15	95.67 ±5.48	p=0.000*

**statistically significant difference; #Fridman's test*

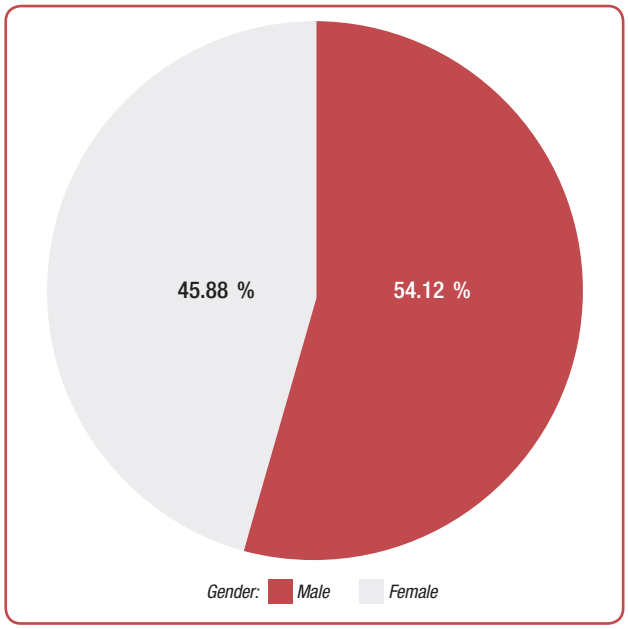

Figure 1: Distribution of subjects by gender of hypertensive patients on monotherapy with trandolapril

Table 2: Orthostatic hypotension and body mass index (BMI) of hypertensive patients on monotherapy with trandolapril

Measurement period	Orthostatic hypotension	BMI		Significance
		< 25	≥ 25	
Prior to treatment	Yes	8 (8.7 %)	17 (10.4 %)	$^{a}p = 0.863$
	No	84 (91.3 %)	146 (89.6 %)	
After 4-6 weeks	Yes	8 (8.7 %)	24 (14.7 %)	$^{a}p = 0.198$
	No	84 (91.3 %)	139 (85.3 %)	
After 12-14 weeks	Yes	9 (9.8 %)	18 (11.1 %)	$^{a}p = 0.621$
	No	83 (90.2 %)	145 (88.9 %)	
After 24-26 weeks	Yes	7 (7.6 %)	9 (5.5 %)	$^{a}p = 0.453$
	No	85 (92.4 %)	154 (94.5 %)	

**statistically significant difference; $^{a}\chi^2$-test; Mann Whitney test;*

During 24-week period after trandolapril introduction into the treatment of hypertension, a statistically significant difference in SBP, DBP and mean BP values was observed (Table 1, Figure 2). From all patients included in the study, 25 (9.8 %) were diagnosed with OH, while 230 (90.1 %) were without OH at first appointment. After initiation of the treatment, on the first visit, 10 patients (3.9 %) still had OH and 22 (8.6 %) new patients had

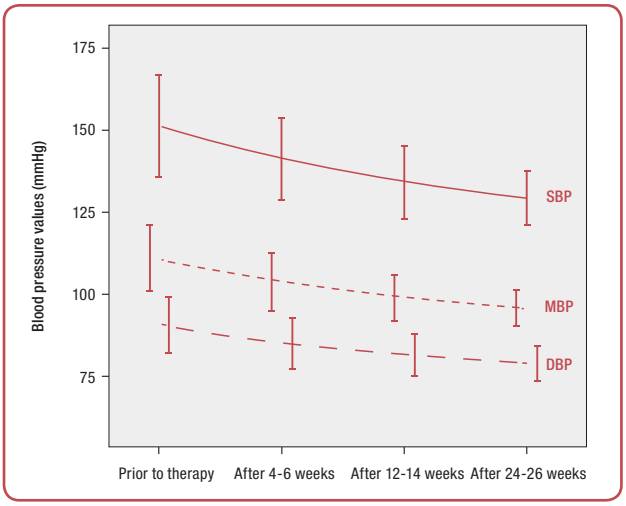

Figure 2: Systolic, diastolic and mean blood pressure of hypertensive patients on monotherapy with trandolapril
**SBP: systolic blood pressure, MBP: mean blood pressure, DBP: diastolic blood pressure;*

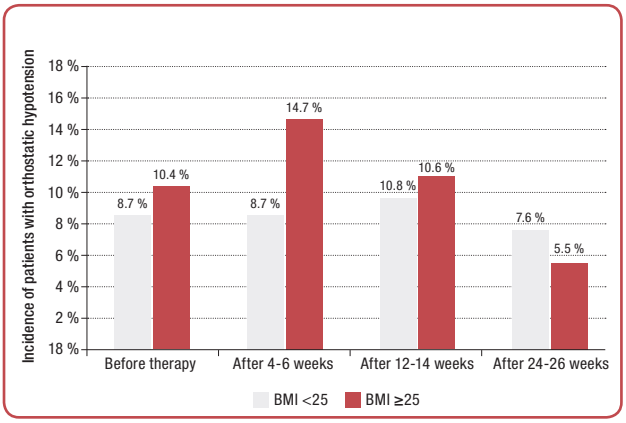

Figure 3: Incidence of orthostatic hypotension in normal weight and overweight patients (on trandolapril therapy)

Table 3: Incidence of adverse effects

Incidence of adverse effects n (%)	Time (weeks)		
	After 4-6	After 12-14	After 24-26
No adverse effects	250 (98.03 %)	250 (98.03 %)	249 (97.64 %)
Mild fatigue	2 (0.8 %)	0 (0 %)	0 (0 %)
Mild occasional a	1 (0.39 %)	0 (0 %)	0 (0 %)
Rare episodes of dry cough	1 (0.39 %)	1 (0.39 %)	1 (0.39 %)
Mild nausea	1 (0.39 %)	0 (0 %)	0 (0 %)
Mild vertigo	0 (0 %)	2 (0.8 %)	1 (0.39 %)
Occasional headache	0 (0 %)	2 (0.8 %)	0 (0 %)
Occasional moderate vertigo	0 (0%)	0 (0 %)	4 (1.56 %)

**Fridman's test;*

OH. There was no significant difference in OH incidence in this period.

Later, at the second visit, there were 7 patients (2.7 %) with prior OH and 20 patients with newly diagnosed OH.

Finally, statistically significant decrease in incidence of OH was recorded after 24-26 weeks of

treatment ($p < 0.05$), within only 6.2 % of subjects with OH.

Regarding the incidence of OH in normal body weight and overweight patients, there was no statistically significant difference (Table 2). However, after 4-6 weeks of follow-up, in the overweight group there was slightly increased incidence of OH, which declined later in the study (Figure 3). Finally, about 1.5 % of the patients experienced one of the side effects of trandolapril (Table 3). Moreover, there were no cases of death in the study.

Discussion

This study has shown a great safety as well as efficiency of trandolapril for treating poorly regulated hypertension. Trandolapril successfully and significantly decreased SBP, DBP and mean BP in all patients during 24 weeks of follow up, with continuous antihypertensive effect throughout this period. Moreover, this research presented a low incidence of side effects of trandolapril, especially of dry cough (0.39 %). Furthermore, there was a significant lowering of OH occurrence between the third and fourth visit. After 24-26 weeks of the treatment and follow up, only 6.4 % of patients had OH. Overall, there was no statistical difference in the incidence of OH regarding BMI. Nevertheless, right after introducing trandolapril to the treatment, there was a slightly higher incidence of OH in overweight patients, but by the end of the study the incidence of OH in overweight and normal weight patients was less than 8 %.

Several studies have shown a difference in hypotensive effect of various ACE inhibitors as a result of their pharmacokinetics.

OH is more frequently found in subjects with diabetes mellitus, followed by a higher incidence of falls, fractures and early death.[8] Beside diabetes, OH is also found in the obese patients, where there is a common occurrence of autonomic dysfunction.[9] Among the reasons for OH occurrence in obese patients is cardiovascular autonomic neuropathy, which can result, in addition to OH, in exercise intolerance, silent myocardial ischaemia.[11] In the obese, a common finding is reduction of sensitivity of the cardiac sinus node, which affects sympathetic and parasympathetic activity.[12, 13]

Some studies also suggest that weight loss can improve autonomic function.[10] On the other hand, a rapid weight reduction can, in some cases of obese diabetics, result in severe OH - an autonomic dysfunction masked by long-standing hypertension and obesity.[14-16]

Occasional occurrence of OH is usually associated with the time of day and drug intake. More commonly OH happens in the morning, requiring several BP measurements to reach an accurate diagnosis. "Table-tilt" test and the "beat-to-beat" BP monitoring are new diagnostic approaches, which enable better quantification of OH.[17]

The mechanism of drug-induced OH can be explained by drugs interfering with reflexes that limit vasoconstriction, the heart rate and minute volume.[18] Numerous studies have demonstrated association of OH with cardiovascular and cerebrovascular morbidity (heart attack, stroke, heart failure).[19] Moreover, causes and mechanisms of OH hypertensive patients and diabetics have not been completely explained.[20] The Malmö Study examined the connection between different cardiovascular risk factors and OH incidence.[21] The ARIC Study showed that OH could bring a significant risk for ischaemic stroke.[22]

Also, analysis of the British Women's Heart and Health Study has shown a significant prevalence of OH in hypertensive patients. According to their findings, ACE inhibitors ere highly correlated with the prevalence of OH in women.[23]

Canney et al examined the impact of different antihypertensive drugs used as a monotherapy on the occurrence of OH in elderly patients with hypertension. It was shown that only beta-blockers had association with long-term and persistent OH.[24] On the contrary, Montastruc et al have shown a lower incidence of OH when ACE inhibitors were used compared to other drugs.[25]

When making a differential diagnosis, initial OH that can occur in the elderly and in the young should be considered. These persons suffer from a short-term and temporary drop in BP when getting to the upright position from the previous lying down position.[26] Finally, it is important to stress out that trandolapril causes a low percentage of OH compared to other ACE inhibitors, both in short-term and long-term use. The absence of OH when using trandolapril was also shown in several other studies.[27, 28]

Conclusion

OH is a common cause of treatment rejection by patients, often leading to treatment modification or even secession in hypertensive patients, which can lead to poor hypertension and cardiovascular risk control. Therefore, it is important to timely recognise, diagnose and adequately treat OH, using both pharmacological and non-pharmacological treatment. As shown in this study, trandolapril, along with some other ACE inhibitors, has shown good balance in hypertension control and OH occurrence. Therefore, they can be used in long-term treatment to prevent OH and improve patient compliance.

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None.

Conflict of interest

None.

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