ORTHOSTATIC HYPOTENSION AND THERAPY WITH AN ACE INHIBITOR IN HYPERTENSIVE PATIENTS

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ORTOSTATSKA HIPOTENZIJA KOD PACIJENATA SA HIPERTENZIJOM NA TERAPIJI ACE INHIBITORIMA

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ABSTRACT

Orthostatic hypotension (OH) is defined as a drop in the systolic blood pressure greater than 20 mmHg and that of the diastolic blood pressure greater than 10 mmHg within 3 minutes from the change of the body's position from lying or sitting down to standing up. The objective of this study is to analyse the incidence and severity of orthostatic hypotension when taking one of the generic representatives of the ACE inhibitor group (trandolapril) as a monotherapy in patients with essential hypertension. The study involved 314 patients (medium age of 54±4 years; 52.5% men) with poorly regulated hypertension for whom trandolapril was introduced as monotherapy. The incidence rates of patients with and without orthostatic hypotension between the first and second examination were not statistically significantly different. At the second control examination, 7 patients (2.3%) still had orthostatic hypotension, as was the case at the first examination. Between the third and fourth controls, a statistically significant decrease in the number of patients with orthostatic hypotension was recorded. No statistically significant difference in the incidence of orthostatic hypotension between patients with normal body mass and those who were overweight was observed. Our study has shown that certain ACE inhibitors, such as Trandolapril, do not have a pronounced adverse effect with regard to orthostatic hypotension and that in long-term application, they can have a positive role in the prevention of hypotensive episodes and improving patient compliance.

Keywords: Hypertension, orthostatic hypotension, ACE inhibitors

SAŽETAK

Ortostatska hipotenzija (OH) se definiše kao pad sistolnog krvnog pritiska za više od 20 mmHg i dijastolnog krvnog pritiska za više od 10 mmHg unutar 3 minute od promene položaja tela iz ležećeg ili sedećeg u uspravni. Cilj rada je ispitivanje učestalosti i težine ortostatske hipotenzije pri upotrebi ACE inhibitora kao monoterapije kod bolesnika sa esencijalnom hipertenzijom. U studiju je uključeno 314 pacijenata (srednje starosti 54±4 godina.; 52.5% muškaraca) sa loše regulisanom hipertenzijom kojima je trandolapril uveden kao monoterapija. Učestalost ispitanika sa i bez ortostatske hipotenzije, između prve i druge kontrole nije se statistički značajno razlikovao. Na drugoj kontroli 7 ispitanika (2,3%) i dalje je imalo ortostatsku hipotenziju kao i na prvoj kontroli. Između treće i četvrte kontrole zabeležen je statistički značajan pad broja ispitanika sa ortostatskom hipertenzijom. Nije uočena statistički značajna razlika u učestalosti ispitanika sa ortostatskom hipertenzijom između normalno uhranjenih i gojaznih ispitanika. Naša studija je pokazala da neki ACE inhibitori poput trandolaprila nemaju izraženo nepovoljan efekat u smislu ortostatske hipotenzije i da u dugotrajnoj primeni mogu imati pozitivnu ulogu u smislu prevencije hipotenzivnih epizoda.

Ključne reči: hipertenzija, ortostatska hipotenzija, ACE inhibitori

INTRODUCTION

Hypertension is not just a disease but also a risk factor for developing cardiovascular and cerebrovascular diseases. Poor control and inadequate treatment of hypertension have resulted in sharp increases in the incidence and prevalence of this disease in Serbia in the past half century. ACE inhibitors are a widespread group of drugs most commonly utilized to treat arterial hypertension, heart failure, conditions occurring post-acute myocardial infarction, diabetes, diabetic and non-diabetic renal disease, left ventricular hypertrophy, and microalbuminuria (1). The mechanism of action for these drugs is based on blocking the angiotensin-converting enzyme (ACE), which, in turn, blocks the conversion of angiotensin I into angiotensin II. The advantage of using ACE inhibitors is evident not only because they decrease the activity of angiotensin II but also because they decrease catecholamine levels and influence vascular remodelling (2). Trandolapril is one of the so-called non-sulphydryl-containing ACE inhibitors. Trandolapril is a prodrug; to exert its effects, it needs to be de-estrified into its active metabolite, trandolaprilat. Trandolaprilat has a high affinity for binding to the ACE; the required concentration for blocking 50% of ACE is lower than those of enalaprilat and captoprilat and is similar to that of ramiprilat (3). When rising from a horizontal position, a small drop in the systolic and a small rise in the diastolic blood pressure normally occur. Orthostatic hypotension (OH) is defined as a drop in the systolic blood pressure greater than 20 mmHg and that of the diastolic blood pressure greater than 10 mmHg within 3 minutes from the change of the body's position from lying or sitting down to standing up (4).

OH can occur in any age and in both sexes, and its prevalence increases with age; its occurrence within the population over 65 years of age is estimated at 5-30% (5). Orthostatic hypotension is a consequence of dysautonomia, which changes the reflex response of the body to postural stress. It can be asymptomatic or accompanied by a range of symptoms. The most common symptoms are dizziness, blurry vision, headache, weakness, palpitations, nausea, and neck pain. It is advised to occasionally measure blood pressure both when lying down and sitting up in all patients above 50 years of age and to gradually introduce hypertension medication (6). Aetiologically, OH is neurogenic or non-neurogenic, while in terms of the timing of the symptoms, it is initial, classic and delayed. Orthostatic hypotension is a significant side effect of some hypertension drugs, including beta-blockers, calcium blockers, ACE inhibitors, and diuretics (7). Keeping in mind the heterogeneous and individual responses of patients suffering from essential hypertension to certain groups of drugs, it is necessary to determine the characteristics of the patients' responses after taking ACE inhibitors in terms of the occurrence of orthostatic hypotension. Analysing the incidence of orthostatic hypotension in certain groups of patients can help with selecting specific drug groups for treating essential

hypertension. The objective of this study is to analyse the incidence and severity of orthostatic hypertension when taking one of the generic representatives of the ACE inhibitor group (trandolapril) as a monotherapy in patients with essential hypertension.

METHODS

This research is part of a multicentric, prospective study conducted in over a 24-week period. The study involved 314 patients (medium age of 54 ± 4 years; 52.5% men) with poorly regulated hypertension for whom trandolapril was introduced as monotherapy.

The definition of poorly regulated hypertension included values of systolic blood pressure ≥ 140 and of diastolic blood pressure ≥ 90 mmHg, measured in two control examinations. The patients were divided into two groups. The first group included patients with stage I arterial hypertension (140/90–149/109 mmHg). The second group included patients with stage II arterial hypertension ($> 150/110$ mmHg).

The study did not include patients younger than 18 years of age, pregnant women (positive β -hCG test), nursing mothers, women of reproductive age with inadequate contraception and the possibility of conception, patients with orthostatic hypotension, patients with serious renal failure, anaemia (haemoglobin < 100 g/L), electrolytic imbalance, heart rhythm disorders, transaminase values 1.5 times higher than reference values, and patients with microalbuminuria > 300 mg/24 h.

All patients were initially given a physical examination: their body weight and height were recorded, their body mass index calculated, a 12-channel EKG conducted, and their heart rate was calculated. Control visits of these patients were conducted after 6, 12 and 24 weeks upon their inclusion in the study. All patient examinations included measurements of blood pressure while sitting and standing and determinations of heart rate. Blood pressure was measured using a mercury sphygmomanometer, placing the cuff to cover 2/3 of the patient's upper arm and including at least 80% of its circumference. Measurements were conducted three times on both arms with one-minute breaks, followed by calculation of the mean value. Each patient's trandolapril dose was corrected at control visits to achieve adequate blood pressure regulation ($\leq 120/80$ mmHg). All patients signed an informed consent before they were included in the study. The study was approved by the Ethics Review Board of the Cardiovascular Institute Dedinje.

Data are described through descriptive statistical methods and were analysed using repeated measures ANOVA calculations. The descriptive statistical methods used in the research included central tendencies measures (arithmetic mean value, median), structure indicators (expressed in percentages) and variability measures (standard deviation, minimal and maximal value).

RESULTS

The study included 314 patients. The average age of the study subjects was $54,41 \pm 11,875$ years. The youngest patient was 28, and the oldest was 88. There were 165 men (52,5%) and 149 women (47,5%) in the test group. No statistically significant difference was observed regarding the incidence of patients of either sex (chart 1). The average BMI value in patients in this group was $26,91 \pm 3,80$, with a range of 16,94 to 37,64. Statistically significant differences in incidence were observed for patients with BMIs both lower and higher than 25. There was a statistically more significant incidence of patients with BMIs equal to or greater than 25 (chart 2). A total of 32,5% patients had BMIs lower than 25, while 67,5% patients had BMIs equal to or greater than 25. Patients were randomized according to hypertension severity into two groups. No statistically relevant differences in the incidence rates of patients with varying degrees of hypertension were observed. In the study group, 152 patients had hypertension of the first degree (48,4%), while 162 patients (51,6%) had hypertension of the second degree (chart 3). At the first control examination, the number of patients with orthostatic hypotension was not statistically significantly different than the number of patients who had orthostatic hypotension before introducing the Trandolapril treatment (chart 4). At the first doctor's appointment, 32 (10,3%) patients had orthostatic hypotension, while 280 patients (89,7%) were without orthostatic hypotension. At the first control examination after the treatment had been introduced (the second doctor's appointment), out of 32 patients who had orthostatic hypotension before Trandolapril treatment, 11 patients (2,3% of the total number of patients) still had orthostatic hypotension, while 31 patients (9,9%) who did not have orthostatic hypotension before the treatment was initiated now had orthostatic hypertension 4-6 weeks into treatment. The incidence rates of patients with and without orthostatic hypotension between the first and second examinations were not statistically significantly different. At the second control examination, 7 patients (2,3%) still had orthostatic hypotension, as was the case at the first examination, while 28 patients who did not have orthostatic hypotension at the first examination now had it at the second control. Between the third and fourth controls, a statistically significant decrease in the number of patients with orthostatic hypotension was recorded (chart 4). Namely, 24-26 weeks into the treatment, orthostatic hypotension was observed only in 6,4% of patients. Seven patients (2,2%) with orthostatic hypotension at the third control examination also had it at the fourth examination, while orthostatic hypotension was observed in 13 patients (4,2%) who did not previously have it. No statistically significant difference in the incidence of orthostatic hypotension in patients with normal body mass and those who were overweight was observed. Upon introducing Trandolapril treatment, a somewhat higher incidence of orthostatic hypotension was observed in patients with BMIs greater than 25, but until

SEX

Chart 1. Distribution of subjects by gender

BMI

Chart 2. Distribution of subjects according to BMI

Severity of hypertension

Chart 3. Distribution of subjects according to severity of hypertension

the end of the monitoring period, the incidence rates of orthostatic hypotension in both groups of patients were less than 10% (chart 5). At the end of the study, 2% of patients suffered from side effects. During the study, there were no deaths among the tested patients (table 1).

DISCUSSION

Our study illustrates the excellent efficiency and safety of Trandolapril use in patients with unregulated hypertension and cardiovascular complications of hypertension. Over 24 weeks, Trandolapril caused significant decreases in systolic, diastolic and mean blood pressure in all patients. The anti-hypertensive effect of Trandolapril was strong and continuous throughout the study period. Our study showed a very low percentage of side effects, with a particularly low incidence of dry cough (0.3%). Our study also revealed a statistically significant decrease in the number of subjects with orthostatic hypotension in the second half of the study period, between the third and fourth control examinations. After 24-26 weeks of treatment, only 6,4% of study subjects had orthostatic hypotension. No statistically significant difference in the incidence of orthostatic hypotension in patients with normal body mass and those who were overweight was observed. Upon introducing Trandolapril treatment, a somewhat higher incidence of orthostatic hypotension was observed in patients with BMIs greater than 25, but until the end of the monitoring period, the incidence rates of orthostatic hypotension in both groups of patients were less than 10%. Several studies have shown that there are differences in the hypotensive effects of different ACE inhibitors, keeping in mind the differences in their pharmacokinetics.

Orthostatic hypotension is more frequent in patients with diabetes mellitus and is accompanied by higher incidence rates of falls, fractures and early death (8). Orthostatic hypotension can occur occasionally depending on the time of day and other medications being taken. The condition is more frequent in the morning and requires taking several measurements to achieve an accurate diagnosis. New diagnostic methods, such as the "table-tilt" test and "beat-to-beat" blood pressure monitoring, enable better quantification of orthostatic hypotension (9). Numerous studies have demonstrated the clinical efficiency and safety of the use of Trandolapril in hypertension treatment. The drug-induced orthostatic hypotension mechanism is connected to the drug's interference with reflexes that lim-

Orthostatic hypotension

Chart 4 Incidence of orthostatic hypotension in patients during trandolapril therapy

Orthostatic hypotension and BMI

Chart 5. Incidence of orthostatic hypotension in patients with normal BMI and obese patients during trandolapril therapy

it vasoconstriction, heart rate frequency or the determination of the minute volume (10). Several studies have shown that orthostatic hypotension is coupled with cardiovascular and cerebrovascular mortality (heart attack, stroke, heart failure) (11). However, the mechanisms of origin

Table 1. Adverse effects

Incidence of adverse effects n (%)	Incidence of adverse effects		
	Time		
	After 4-6 weeks	After 12-14 weeks	After 24-26 weeks
No adverse effectsa	299 (98,7%)	296 (98,3%)	299 (98,0 %)
Mild fatigue	1 (0,3%)	0 (0%)	0 (0%)
Mild occasional a	1 (0,3%)	0 (0%)	0 (0%)
Rare episodes of dry cough	1 (0,3%)	1 (0,3%)	1 (0,3%)
Mild nausea	1 (0,3%)	0 (0%)	0 (0%)
Mild vertigo	0 (0%)	2 (0,7%)	1 (0,3%)
Occasional haedache	0 (0%)	2 (0,7%)	0 (0%)
Occasional moderate vertigo	0 (0%)	0 (0%)	4 (1,3%)

#Fridman-ov test

for orthostatic hypotension in patients with hypertension and diabetics have not yet been fully explained (12). The Malmö Study on prevention has especially looked into the connection between the risk factors and the occurrence of orthostatic hypotension (13). The study determined that, apart from hypertension and diabetes, other factors, such as smoking, age and positive patient history for cardiovascular disease, were coupled with an increased incidence of orthostatic hypotension. The ARIC Study showed that orthostatic hypotension was coupled with a considerable risk of ischaemic stroke in all age categories (14). The analysis of a large “British Women’s Heart and Health Study” showed that there is a considerable prevalence of orthostatic hypotension in patients with hypertension (15). The prevalence of orthostatic hypotension in women between 60 to 80 years of age is 28%; systolic orthostatic hypotension was more frequent than diastolic orthostatic hypotension (20.4% vs. 12.4%). A higher correlation between the use of ACE inhibitors and the prevalence of orthostatic hypotension in women over 65 years of age has been shown. A large study by Irish authors looked into the effects of monotherapy for hypertension (ACE inhibitors, beta-blockers, calcium blockers and diuretics) on the prevalence of orthostatic hypotension in older patients with hypertension. The research showed that only monotherapy with beta-blockers was coupled with long-term and persistent orthostatic hypotension (16). A group of French authors demonstrated a higher occurrence of orthostatic hypotension with the use of diuretics and calcium blockers, while ACE inhibitors were not connected to a significant postural drop in blood pressure (17). In differential diagnosis, we have to discern persistent orthostatic hypotension from the condition called initial orthostatic hypotension, which can occur at both young and old ages. Affected individuals are persons who suffer from a transitory (up to 15 seconds) drop in blood pressure when moving from lying down to an upright position (18). The pathophysiological cause for this condition is a temporary imbalance between the minute volume and the peripheral vascular resistance. Finally, it is important to note that in both short- and long-term use, Trandolapril is characterized by a low incidence of orthostatic hypotension, unlike other ACE inhibitors. Several other studies have also shown the absence of orthostatic hypotension with the use of Trandolapril (19, 20).

CONCLUSION

Although treatment for hypertension is an important step in reducing cardiovascular risk, orthostatic hypotension and its symptoms are important causes of poor compliance and inadequate treatment. Careful diagnosis of orthostatic hypotension in patients with hypertension is necessary, as is the adequate application of both non-pharmacological and pharmacological measures with the aim of both mitigating and treating the condition. Our study has shown that certain ACE inhibitors, such as Trandolapril,

do not have a pronounced adverse effect with regard to orthostatic hypotension and that in long-term application, they can have positive roles in the prevention of hypotensive episodes and improving patient compliance.

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