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THE TREATMENT OF HYPERTENSION WITH TELMISARTAN IN THE SPHERE OF CIRCADIAN RHYTHM IN METABOLIC SYNDROME IN THE ELDERLY

V. FORMOSA, A. BELLOMO, A. IORI, V. GIANTURCO, E. D'OTTAVIO, M. MANCINELLA, C. LO IACONO, G. TROISI, V. MARIGLIANO*

Dipartimento di Scienze dell'Invecchiamento, "Sapienza" Università di Roma, Umberto I Policlinico di Roma, Viale Del Policlinico 155, I-00161 Roma, Italy;

*Corresponding author:
Phone:+(39-06)-445-3600 Fax: +(39-06)-445-6316
E-mail: vincenzo.marigliano@uniroma1.it

ABSTRACT

This study compares the efficacy of telmisartan with that of valsartan and ramipril in reducing blood pressure (BP) over 24 hrs in the elderly patients with metabolic syndrome (MS). This prospective and open label study analyzed a sample of 60 patients over 65 years of age with hypertension and with MS. At the beginning the BP was monitored by a 24-hr ambulatory blood pressure monitoring (AMBP). Following this, the 60 patients were divided into 3 groups of 20, to each of which was prescribed, respectively, telmisartan, valsartan and ramipril to take for 12 weeks. The drugs were to be taken at 9.00 a.m. Later on the doses were increased. After 12 weeks of therapy, BP was monitored by a 24-hr AMBP. The use of telmisartan caused a greater reduction of the BP in the final 4-6 hours of the period between the 1st administration of the drug and the next one, these last 4-6 hours being those when cardiovascular and cerebrovascular accidents are more frequent (between 6.00 and 10.00 a.m.). Comparing to valsartan and ramipril, telmisartan results in excellent pressure control during the last 4-6 hours between the 1st administration of the drug and the next one.

Keywords: telmisartan, valsartan, ramipril, blood pressure, metabolic syndrome,

INTRODUCTION

The prevalence of MS in Italy is 23% for men and 23% for women (CCM, 2009), while it becomes 29% for men and 37% for women over 65 years of age, i.e., it is quite common in the elderly.

The aim of this study was to compare the reduction of BP during the 24 hours subsequent to the administration, with particular interest to the last 4-6 hours of this period, of telmisartan, valsartan and ramipril, in the elderly with MS, during an interval of a 12-week therapy. The drugs were to be taken at 9.00 a.m. These 3 drugs were chosen for the study because telmisartan and valsartan are angiotensin-II-receptor blockers (ARBs), while ramipril is an inhibitor of angiotensin-converting enzyme (ACE), and these are the

pharmacological classes recommended as first choice for the treatment of MS in the European Society of Hypertension (ESH), the European Society of Cardiology (ESC) 2007 Guidelines (Mansia et al., 2007). Other important characteristics of telmisartan are its long half-life (24 hours) (Gosse, 2006) and its proven good tolerability (Smith, 2008). Valsartan was chosen because it belongs to the ARB class, as telmisartan, so to compare two drugs of the same class, while ramipril was chosen because it is one of the most prescribed drugs in Italy for hypertension (OSMED, 2008).

SUBJECTS AND METHODS

This study is prospective and open label and its population comprises 60 patients over 65 years of age with hypertension at grades 1, 2 or 3 according to the ESH/ESC 2007 Guidelines (Mansia et al., 2007), and with MS, diagnosed according to the guidelines of the National Cholesterol Education Program Adult Treatment Panel III proposed by the American Heart Association (AHA) in 2005 (Grundy et al., 2005). Patients had a first access to the Geriatric Day Hospital where their anamnesis was taken, and a physical examination was also performed. The patients group was selected after checking the cholesterol, triglyceride and glucose blood level, and after checking their kidney and liver functions. BP of each patient was measured by an aneroid sphygmomanometer and their waist circumference was determined using a measuring tape. Before BP measurement, patients rested for 5 minutes without distractions. BP was measured while patients were sitting in a chair that supported their back and beside a table that supported their arm, so that it rested at heart level. BP was measured 2 times and the second time was after 2 minutes; if the 2 results were very different, it was measured a third time and their average was calculated.

To determine waist circumference, a measuring tape was located between the iliac crest and the inferior border of the rib cage and the tape was placed around the waist in horizontal.

Patients with a history of coronary illness, cardiac failure or strokes, as well as with hepatic or renal insufficiency or with secondary hypertension were excluded. Patients who used pharmaceutical products which might influence the BP such as the β-agonists and antagonists, nitroglycerine, teophyllin, inhibitors of monoamine oxidase, phenothiazine, tricyclic antidepressants and other antihypertensive drugs were excluded, too. Once the group of patients has been selected, the BP was monitored by a 24-hr AMBP. Following, 60 patients were chosen, and after they were divided into 3 groups of 20, to each of which was

prescribed respectively, 40 mg (1 tablet)/day of telmisartan, 80 mg (1 tablet)/day of valsartan, and 2.5 mg (1 tablet)/day of ramipril, to take for 2 weeks. The drugs were to be taken at 9.00 a.m. Later on, after a sphygmomanometer measurement to control the BP levels reached by the patients, the dose of ramipril was increased to 5 mg (1 tablet)/day, if it was deemed necessary. After 2 weeks, once more after checking the BP levels reached by the patients using the sphygmomanometer, the doses were increased to 80 mg (1 tablet)/day of telmisartan, 160 mg (1 tablet)/day of valsartan and 10 mg (1 tablet)/day of ramipril. The patients were treated in this way for a period of further 8 weeks at the end of which their BP was monitored by a 24-hour AMBP. So this study had a total duration of 12 weeks.

Comparing for every patient the two AMBP data obtained at the beginning and after 12 weeks of therapy, the reduction of BP obtained in each of the 24 hours of the interval between one administration of the drug and the next was calculated; at a later stage the average reduction of the blood pressure for each group being treated was calculated for every hour of the day and for 24 hours, for the first 18 hours and for the last 4-6 hours of the interval between one administration of the drug and the next (considering the time of the first administration of the medicine as 0 hour).

RESULTS

The average BP reduction in the 24 hr between one administration of the drug and the next was 13.8 (systolic pressure) and 9.5 (diastolic pressure) mmHg, considering the terlmisartan-treated patients (Group 1), 11.5/8.0 mmHg considering the valsartan-treated patients (Group 2) and 11.8/7.5 mmHg considering the ramipril-treated patients (Group 3). The average BP reduction in the first 18 hours of the interval was 14.55/9.9 mmHg in the Group 1, 13.2/8.8 mmHg in the Group 2 and 13.0/8.3 mmHg in the Group 3, while the average reduction in the last 6 hours was 11.7/8.3 mmHg in the Group 1, 9.0/5.7 mmHg in the Group 2 and 8.3/5.3 mmHg in the Group 3. The most important difference was in the BP reduction during the last 4 hours, that was 12.5/8.5 mmHg in the Group 1, 8.9/5.6 mmHg in the Group 2 and 8.5/5.4 mmHg in the Group 3. The patients treated with these 3 drugs showed no side effects.

DISCUSSION

Actually it is very important to prescribe the anti-hypertensive drug that is most indicated for every subject, and it is not a simple decision. It is particularly difficult to treat an

elder patient, too (Rang et al., 2005). So it is important that an anti-hypertensive drug is characterized by a good efficacy in reducing global cardiovascular risk (Giampaoli et al., 2005), by a good efficacy in case of comorbidity and by a high tolerability (Smith, 2008) . It has to be characterized by a high compliance (Chrysant et al., 2005) and it could be used in association with other anti-hypertensive classes of drugs, if necessary (Francischetti et al., 2008). Often an elder patient with cognitive deficit forgets to take drugs, and this can be reduced using drugs in mono-administration; but this mono-administration has to control hypertension during the 24 hours between one administration and the next. Another important aspect to consider is the cost of a drug, because in Italy the elderly are the persons with lower income (ISTAT, 2006).

The ONTARGET® study (Mann et al., 2008) shows that telmisartan reduces global cardiovascular risk and the MICADO study (Matsuo et al., 2007) shows that this drug has a long duration of action in the 48 hours interval between one administration and the next. too, when a patient forgets to take a dose, and it is frequent in the elderly. Telmisartan is characterized by a duration of action longer than the other drugs of the same class, and so it can determine a significant reduction of BP if used in mono-administration, and it is important in the elderly. This drug can be used in association with hydrochlorotiazide if necessary, while the utility of its use in association with ACE inhibitors is discussed (Mann et al., 2008). It is characterized by a high tolerability and compliance, in fact this study showed no side effects, and it can be used in patients with comorbidity, as it is shown in this study, too. But it can cause often hypotensive symptoms (Mann et al., 2008) and it has a high cost.

Telmisartan is a partial agonist of the peroxisome proliferator-activated receptor gamma (PPAR gamma) (Benson et al., 2004) and so it influences glycemia, low density lipoproteins (LDL) and high density lipoproteins (HDL) cholesterol and triglyceride blood levels (Vitale et al., 2005) and insulin resistance (Yamagishi and Takeuchi, 2005), i.e., it is important in patients with MS. As other drugs of the same class, telmisartan influences proteinuria (Berl, 2009) and left ventricular hypertrophy (Prisant, 2008). So it can be considered an important alternative to ACE inhibitors in the elder patient therapy.

When making a decision about the therapy to administer to an elder patient with MS, it is important to consider all the aspects analyzed and guidelines but also the experience of each physician. Besides, non-pharmacological therapy has to be considered with the

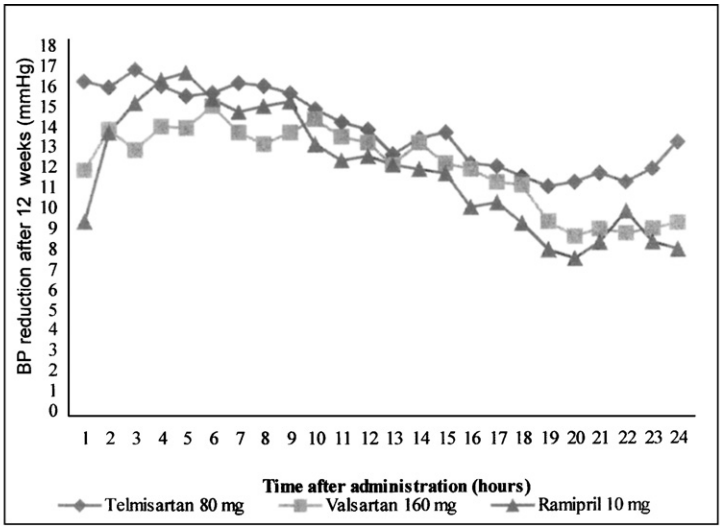

Figure 1. Systolic BP reduction of the 3 groups of patients after 12 weeks of therapy. The administration of the drug is considered as hour 0.

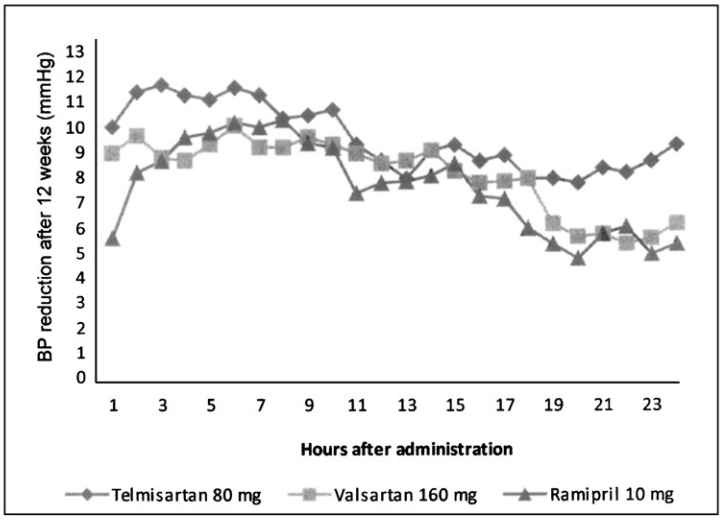

Figure 2. Diastolic BP reduction of the 3 groups of patients after 12 weeks of therapy. The administration of the drug is considered as hour 0.

pharmacological one: physical exercise (Bonetti, 2001), equilibrated diet (Panico et al., 2008), cessation of smoking (Chelland Campbell et al., 2008).

In the future more studies about MS in the elderly have to be done, because there are not enough studies that examine only this category of persons and its different characteristics.

CONCLUSIONS

This study shows that the use of telmisartan causes a greater reduction of systolic and diastolic BP in the final 4-6 hours of the period between the 1st administration of the drug and the next one, than the other two drugs (Figures 1, 2), these last 4-6 hours when cardiovascular and cerebrovascular accidents are more frequent (between 6 and 10 a.m.) (Cohen et al., 1997). For the last 4 hours of the interval telmisartan is 2.7/2.6 mmHg more effective than valsartan and 3.4/3.0 mmHg more effective than ramipril in reducing BP.

CONFLICT OF INTEREST STATEMENT: None.

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