

COMPARATIVE STUDY REGARDING CELIPROLOL AND METOPROLOL USE IN THE TREATMENT OF ESSENTIAL ARTERIAL HYPERTENSION

SORINA LIVIA POP^{1*}, CODRUȚA MĂRGINEAN¹, SIMONA MIREL²,
DANIEL MUREȘAN¹, DANIELA POP VORNICESCU¹, RAREȘ
GHERMAN¹, EMIL ONACĂ¹

“Iuliu Hatieganu” University of Medicine and Pharmacy, Cluj-Napoca

¹*Faculty of Medicine*

²*Faculty of Pharmacy*

** corresponding author: sorinacdt@yahoo.com*

Abstract

The effects of β -blockers in essential arterial hypertension (EAHT) are well known. The main objective of our study was to study comparatively the efficacy and the safety of the administration of two representatives of this class: celiprolol *versus* metoprolol, in equivalent doses, over a 2 weeks period. Unlike metoprolol, celiprolol is a cardioselective beta 1-blocker, with a moderate intrinsic beta 2-sympathomimetic action and minimal vasodilatory effects. Metoprolol and celiprolol were initially administered in doses of 6.25 mg twice a day and 50 mg a day, respectively; the doses were increased every 3 days, under careful clinical monitoring, up to 50 mg twice a day and 200 mg a day, respectively, a normalization of blood pressure values being obtained. We also monitored the occurrence of the most frequent side effects of beta-blockers: bradycardia, fatigue, cold extremities. Only minor side effects were registered, which did not require the suppression of treatment. No significant changes in laboratory tests were found.

Rezumat

Efectele substanțelor β -blocante în hipertensiunea arterială esențială (HTAE) sunt bine cunoscute. Obiectivul principal al studiului nostru a fost de a studia comparativ eficacitatea și siguranța administrării a doi reprezentanți ai acestei clase: celiprolol *versus* metoprolol, în doze echivalente, pe o perioadă de două săptămâni. Spre deosebire de metoprolol, celiprolol este un cardioselectiv beta 1-blocant, cu o acțiune beta2- intrinsecă, simpatomimetic moderat și cu efecte minime vasodilatatoare. Metoprolol și celiprolol au fost administrate inițial în doze de 6,25 mg de două ori pe zi și respectiv 50 mg pe zi; dozele au fost crescute la fiecare trei zile, sub atentă monitorizare clinică, până la 50 mg de două ori pe zi și respectiv, 200 mg pe zi, și a fost obținută o normalizare a valorilor tensiunii arteriale. Am monitorizat, de asemenea, apariția celor mai frecvente efecte secundare ale beta-blocante: bradicardie, oboseală, extremități reci. S-au înregistrat efecte secundare minore, care nu necesită suprimarea tratamentului. Nu au fost găsite modificări semnificative ale testelor de laborator.

Keywords: β -blockers, celiprolol, metoprolol, essential arterial hypertension (EAHT).

Introduction

Essential arterial hypertension (EAHT) is a major cause of morbidity and mortality, which affects approximately 1 billion people worldwide [1-4].

Non-pharmacological treatment should be supplemented with specific pharmacological treatment for each patient, depending on the associated disorders or particular conditions such as pregnancy and breast feeding. Individual sensitivity and response to pharmacological compounds should also be considered. The high frequency of complications requires the early diagnosing and initiation of the adequate treatment, which can be easily performed today, with minimal costs [4, 5, 7].

In elder hypertensive patients, β -blockers have been found to reduce the incidence of cerebrovascular accidents and acute myocardial infarction [2, 7]. Treatment with β -blockers in EAHT can be associated with diuretics, calcium channel antagonists, α -blockers and drugs that act on the central nervous system (CNS) or on the peripheral nervous system [6, 8, 10, 11].

Starting from this premise, we aimed to evaluate under ambulatory conditions the efficacy and the safety of therapy, the symptoms and side effects in the case of the treatment with celiprolol *versus* metoprolol on patients with EAHT [9, 10].

Materials and Methods

The study included 70 patients, with known EAHT, under treatment with equivalent doses of celiprolol or metoprolol (in monotherapy or combined therapy with other hypotensive drugs) over a 2 weeks period, after each of them signed an informed consent. The study was conducted in accordance with the WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects being approved by the Ethical Commission of the University of Medicine and Pharmacy of Cluj-Napoca.

The demographic characteristics and the treatment peculiarities of the patients included in the study are found in Tables I and II, and the associated risk factors are shown in Figure 1. The patients were divided in two groups: **group I** - including patients under treatment with metoprolol, in monotherapy or combined therapy with other hypotensive drugs; **group II** – including patients under treatment with celiprolol, in monotherapy or combined therapy with other hypotensive drugs.

Table I
Structure of the total studied group

Number of patients		70
Origin		Urban
Mean age		55.82 years
Sex distribution	Men	27
	Women	43
Age group distribution	30 - 39 years	5
	40 - 49 years	16
	50 - 59 years	24
	60 - 69 years	16
	70 - 79 years	9

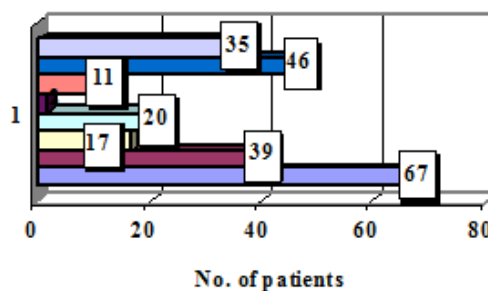


Figure 1

Risk factors for the studied groups

Table II
Structure of groups I and II

GROUP I – under treatment with:	
Ia - Metoprolol = M	
Ib - Metoprolol + ACEI (angiotensin converting enzyme inhibitor) = M + ACEI	
Ic - Metoprolol + Indapamide (I) = M + I	
Id - Metoprolol + ACEI + Indapamide (I) = M + ACEI + I	
Subgroups	No. of patients
Ia	14
Ib	10
Ic	8
Id	5
GROUP II – under treatment with:	
IIa - Celiprolol = C	
IIb - Celiprolol + ACEI = C + ACEI	
IIc - Celiprolol + Indapamide (I)= C + I	
IId -Celiprolol + ACEI + Indapamide (I)= C + ACEI + I	
Subgroups	No. of patients
IIa	12
IIb	9
IIc	8

The *inclusion* criteria were: patients with EAHT diagnosed in the last six months; age between 30 and 80 years. The *exclusion* criteria were: secondary arterial hypertension, obstructive bronchial disease (or other contraindications to β -blocking therapy) and pregnancy.

The following parameters were monitored: the presence of risk factors for arterial hypertension (heredity, obesity, diabetes mellitus, smoking, alcohol consumption), the type of hypotensive treatment (monotherapy or combined therapy), the efficacy of therapy (by comparing initial values, at the beginning of treatment, to values after 2 weeks of treatment), the degree of attainment of the *target values* recommended by international guidelines, and the appearance of side effects of metoprolol or celiprolol medication [9, 10, 11].

We considered the hypotensive therapy effective when blood pressure values were lower than 140/90 mmHg in patients without associated diabetes mellitus, and lower than 130/80 mmHg in patients with diabetes mellitus diagnosed in the last 3 months [2, 7, 9, 10, 11].

Statistical analysis

The results were statistically analysed using the *Microsoft Office 2003* software, and the comparison of results and the evaluation of their statistical significance were performed in *Microsoft Excel* using the *Data Analysis* module and the *Chi-square* test (*Chi-test*). We considered as statistical significance $p < 0.05$.

Results and Discussion

For the patients included in the study, the analysis of cardiovascular risk factors associated with EAHT showed the following: 4.29% (3 patients) had no associated risk factor; 95.71% (67 patients) had one or more associated risk factors. Thus: 24.28% (17 patients) had only one risk factor, 42.86% (30 patients) had 2 associated risk factors, 20% (14 patients) had 3 associated risk factors and 8.57% of all patients (6 subjects) had hypertension and more than 3 associated risk factors. Of risk factors: 67 patients had hereditary EAHT; 39 were obese (a body mass index ≥ 30); 17 patients were diagnosed with diabetes mellitus; 20 patients were smokers, and 2 patients admitted that regularly consumed alcohol. Of all patients with EAHT associated with one or more risk factors, 46 (65.72%), 21 men and 25 women, also had hypercholesterolemia (the other patients having cholesterolemia values ≤ 200 mg/dL). Another risk factor taken into consideration was the serum high density lipoprotein (HDL) cholesterol value. We considered as HDL normal values, for both, men and women, blood values > 45 mg/dL. Thus, 43 (61.42%) patients (21 men and 22

women), had HDL cholesterol values between 35 – 45 mg/dL. Of all the 43 patients, 32 (45.71%) had a low cardiovascular risk, and 11 (15.71%) had a high cardiovascular risk. We found that 63.63% (7 cases) of patients with a high cardiovascular risk were men, and 36.37% (4 cases) were women. The group of patients with a low cardiovascular risk included 56.25% (18 cases) women and 43.75% (14 cases) men. Another studied risk factor was hypertriglyceridemia (according to *The American Heart Association*, pathological values ≥ 150 mg/dL) [10].

Thus, in the studied group, 35 patients (50%) had normal triglycerides values, and 35 (50%) had values higher than 150 mg/dL. Of all patients, 14.29% (10) had *border* values, 30% (21) had a moderate risk, and 5.71% (4) had a high risk, with triglycerides values > 500 mg/dL. In the category of risk factors, we also studied overweight and/or obesity.

The criteria according to which a patient was considered as normal weight, overweight or obese were: height, weight, waist circumference (measured with patient standing) and body mass index (BMI).

Thus: 34.29% (24 patients) were normal weight, 35.71% (25 patients) were overweight, and 30% (21 patients) were obese. 20% (14 patients) had first degree obesity and 10% (7 patients), second degree obesity. Of all the 27 men: 29.63% (8 patients) were normal weight, 29.63% (8 patients) were overweight, 25.93% (7 patients) had first degree obesity, and 14.01% (4 patients) had second degree obesity. In the case of women: 37.21% (16 patients) were normal weight, 39.53% (17 patients) were overweight, 6.28% (7 patients) had first degree obesity, and 6.98% (3 patients) had second degree obesity.

Diabetes mellitus as a risk factor was present in 17 patients (24.29% of all patients) - in 11 (15.72%) men and 6 (8.57%) women.

Approximately 1/3 of all patients with EAHT were on metoprolol or celiprolol monotherapy (37.14% = 26 patients), and 62.86% (44) were on complex hypotensive therapy: 50% (35 patients) on bitherapy, i.e. 27.14% (19 patients) under treatment with metoprolol or celiprolol associated with an angiotensin converting enzyme inhibitor (ACEI), and 22.86% (16 patients) under treatment with metoprolol or celiprolol associated with indapamide; 12.86% (9 patients) were under triple therapy: metoprolol or celiprolol associated with indapamide and an angiotensin converting enzyme inhibitor (in equivalent doses).

In **group I**, the mean systolic blood pressure (SBP) value was 161.62 mmHg, and the mean diastolic blood pressure (DBP) value was 98.78 mmHg. These values were found at the first examination, at the beginning of the study. In **group II**, SBP was 164.39 mmHg, and DBP was 100.6

mmHg. These values were also recorded at the first examination. The analysis of the initial blood pressure values in the two groups of patients shows that in **group II** the mean SBP value was 2.77 mmHg higher than in **group I**, and the mean DBP value was 1.82 mmHg higher compared to the same group. This difference was statistically insignificant ($p = 0.21$).

In **group II**, after 2 weeks of treatment, a 31.91 mmHg decrease in the mean SBP values (from 164.39 mmHg to 132.48 mmHg) and a 15.03 mmHg decrease in DBP (from 100.6 mmHg to 85.57 mmHg) were found. A comparison between the two groups after 2 weeks of treatment showed a higher decrease in the mean SBP value in **group II** (31.91 mmHg, compared to 26.08 mmHg in **group I**), and a higher decrease in the mean DBP value in **group I** (15.81 mmHg) compared to **group II** (15.03 mmHg). This difference in the mean SBP and DBP values between the two groups is not statistically supported, p having a value higher than 0.05 (Figure 2).

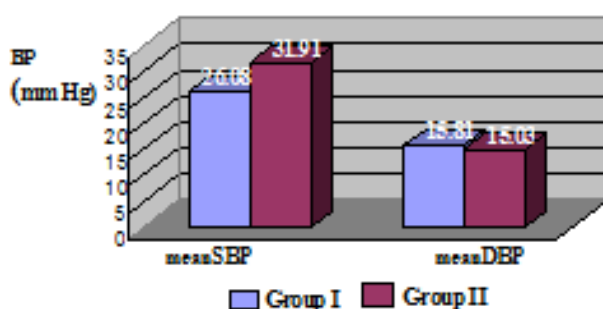


Figure 2

The values of the differences of SBP and DBP measured initially and after 2 weeks of treatment ($p > 0.05$)

In **group I**, we found a decrease in the mean SBP value ranging between 20 mmHg and 30.5 mmHg. Thus: in subgroup **Ia** – the mean SBP value decreased to 23.57 mmHg; in subgroup **Ib** – the mean SBP value decreased to 30.5 mmHg; in subgroup **Ic** – the mean SBP value decreased by 28.75 mmHg, and in subgroup **Id** – the mean SBP value decreased to 20 mmHg (Figure 3).

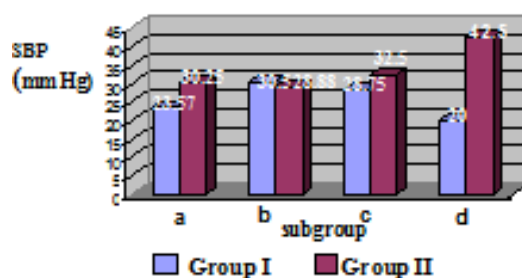


Figure 3

The values of the differences of SBP measured initially and after 2 weeks of treatment ($p=0.046$)

In the subgroups of **group I**, we found a decrease in the mean DBP value ranging between 14 mmHg and 16.88 mmHg. Thus, in subgroup **Ia** – the mean DBP value decreased after 2 weeks of treatment by 16.43 mmHg; in subgroup **Ib** – the mean DBP value decreased by 14 mmHg, in subgroup **Ic** – the mean DBP value decreased by 16.88 mmHg, and in subgroup **Id** – the mean DBP value decreased by 16 mmHg (Figure 4).

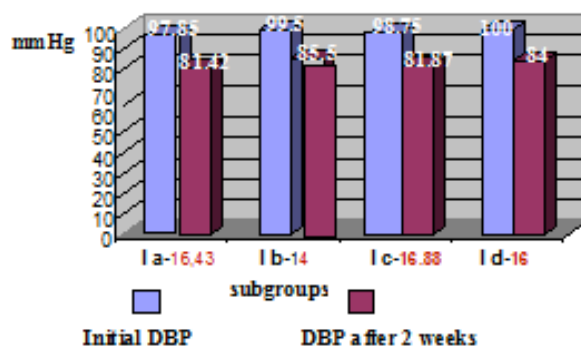


Figure 4

Decrease in the mean DBP value in subgroups of group I

In the subgroups of **group II**, we found a decrease in the mean DBP value ranging between 11.34 mmHg and 21.25 mmHg. Thus, in subgroup **IIa** – the mean DBP value decreased after 2 weeks of treatment by 11.34 mmHg; in subgroup **IIb** – the mean DBP value decreased by 17.22 mmHg; in subgroup **IIc** – the mean DBP value decreased by 15 mmHg, and in subgroup **IId** – the mean DBP value decreased by 21.25 mmHg (Figure 5).

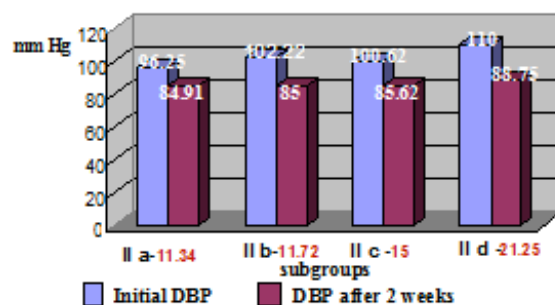


Figure 5

Decrease in the mean DBP value in subgroups of group II

The analysis of the mean DBP values in the two groups shows a higher decrease for metoprolol, in the case of monotherapy, compared to celiprolol in monotherapy (by 5.09 mmHg). For combined therapy with ACEI, a 3.22 mmHg higher decrease was found in subgroup **IIc** (celiprolol + indapamide) of **group II**. In **group II**, there was a 1.88 mmHg higher decrease in the mean SBP value compared to **group I**. In subgroup **Id**, the decrease in the mean DBP value was 5.25 mmHg higher than in **group II**, for the same subgroup (**IId**). However, the difference was not statistically significant (mainly due to the small number of cases studied): $p=0.43$ using the *CHI-square* test and $p=0.21$ using the *CHI-test*.

If initially, all patients had higher blood pressure values than those indicated by arterial hypertension guides, after 2 weeks of treatment, 72.97% (27 patients) in group I and 69.70% (23 patients) in group II reached the target values.

Following treatment, the presence of side effects was observed: 3 patients in group I and 1 patient in group II had bradycardia; 5 patients in group I and 1 patient in group II presented fatigue, and 6 patients in group I and 1 patient in group II had cold extremities.

Conclusions

The majority of the patients included in the study (95.71%) had at least one associated risk factor. The most frequently associated risk factor for 65.75% of patients was hypercholesterolemia (total cholesterol serum value > 200 mg/dL). There were no statistically significant differences in the intensity of the hypotensive effect between the two beta-blockers used. The hypotensive effect was much more intense in the case of severe EAHT forms (higher doses, associated therapy). The appearance of side effects was

less common in the case of the use of celiprolol, both alone and in therapeutic combinations.

References

1. Anderson E. A., Sinkey C.A., Lawton W., Mark A.L. Elevated sympathetic nerve activity in borderline hypertensive humans. Evidence from direct intraneural recordings. *Hypertension*, 1999; 14: 177-183.
2. Black H.R., Elliott W.J., Baseline characteristics and elderly blood pressure control in the Convince trial. *Hypertension*, 2001; 37: 12-18.
3. Gaffney S.M., Denus S., Olson K.L., Key Articles and Guidelines in the Management of Hypertension: 2008 Update. *Pharmacotherapy*, 2008; 28(8): 1041-1058.
4. Gherasim L. Medicina internă, vol. 2, Editura Medicală 2001; 770-795.
5. Harrison. Principiile medicinei interne, ediția a XIV-a, Editura Teora 2001; vol. 1: 224-227, 1523-1538.
6. Iovanov R.I., Tomuța I., Leucuța S.E. Influence of some formulation factors on the release of felodipine from extended release hydrophilic matrix tablets. *Farmacia*, 2009; 57(5): 582-589.
7. Perloff D., Sokolow M., Cowan R., The pronostic value of ambulatory blood pressure monitoring in treated hypertensive patients. *Hypertension*, 1991; 9(1): 33-40.
8. Psaty B.M., Manolino T.A., Use of antihypertensive medications in older adults. *Arch. Intern. Med.*, 2002; 162: 2325-2332.
9. Prasacu I., Mircioiu C., Sandulovici R., Enache F., Release of metoprolol from solid dosage forms. Choice and validation of theoretical model. *Farmacia*, 2009; 57(1): 89-98.
10. Reboldi G., Gentile G., Angeli F., Verdecchia P., Exploring the optimal combination therapy in hypertensive patients with diabetes mellitus. *Expert Rev. Cardiovasc. Ther.*, 2009; 7(11): 1349-1361.
11. The Seventh Raport of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. *J.A.M.A.*, 2003; 289(19): 2560-2570.

Manuscript received: January 2010