

THE EFFICIENCY OF METOPROLOL TARTRATE IN THE TREATMENT OF PURE ARTERIAL HYPERTENSION AT PATIENTS WITH CORONARY ARTERY DISEASE AND THE RISK FACTORS ASSOCIATED

DANIEL LAURENTIU COZLEA¹, DAN MIRCEA FĂRCAȘ^{1*}, CAMIL VARI², ARTHUR-ATILLA KERESZTESI³, RAMONA ȚIFREA¹, LAURENTIU COZLEA¹, GRIGORE DOGARU⁴

¹*Clinica Medicală III, University of Medicine and Pharmacy of Târgu-Mureș, Romania*

²*Discipline of Pharmacology, University of Medicine and Pharmacy of Târgu-Mureș, Romania*

³*Institute of Legal Medicine, Târgu Mureș University of Medicine and Pharmacy, Romania*

⁴*Department of Nephrology, University of Medicine and Pharmacy of Târgu-Mureș, Romania*

**corresponding author: danmircearo@gmail.com*

Abstract

The aim of the present study was to evaluate the efficiency of metoprolol tartrate of various concentrations in the treatment of patients with diverse forms of hypertension - pure, with comorbidities and/or complications (coronary artery disease, heart failure), in the absence of contraindications for the use of betablockers.

The study was performed at the Medical Clinic Nr. 3 - Cardiology of Târgu Mureș, between June 1st 2009 - September 1st 2010, involving a group of 200 patients, 128 men and 72 women, with an average age of 51.7 ± 7.2 years (32-77 years), diagnosed with hypertension (HT), without prior antihypertensive medication - 116 patients, or with a history of hypertension (1-15 years at the moment of diagnosis) and various ambulatory therapeutic schemes of questionable efficiency - 84 patients, in which the ambulatory treatment could not lower blood pressure values below 150/90 mmHg.

Based on our results we consider that the administration of metoprolol tartrate in various concentrations is indicated in all hypertensive patients, in the absence of contraindications for the use of betablockers. Our study concluded that monotherapy is efficient mainly in young patients and patients with recently diagnosed HT with or without treatment, provided the treatment is maximum 4-5 years old, and the patient has not been given betablockers before. Older patients, with comorbidities or HT related complications need an association of drugs in 80% of cases, excluding the medication used in the treatment of comorbidities or complications. As far as the cost-efficiency ratio is concerned, the examined drug deserves a maximum number of points in both regards,

Rezumat

Scopul prezentului studiu a fost de a evalua eficiența metoprololului tartrat în diverse concentrații, în tratamentul hipertensiunii arteriale (HTA) la pacienți cu diverse

forme de HTA, pură, cu comorbidități și/sau cu complicații (boala coronariană, insuficiența cardiacă), care nu au prezentat contraindicații de tratament cu betablocante.

Studiul s-a desfășurat la Clinica Medicală III - Cardiologie, Târgu-Mureș, în perioada 1 iunie 2009 - 1 septembrie 2010, pe un lot de 200 de pacienți, 128 bărbați și 72 femei cu o vârstă medie de $51,7 \pm 7,2$ ani (32-77 ani), diagnosticați cu HTA, fără tratament antihipertensiv în antecedente – 116 pacienți, sau cu hipertensiune arterială veche (1 - 15 ani de la diagnosticare), cu diferite scheme terapeutice ambulatorii cu eficiență îndoielnică - 84 de pacienți, la care tratamentul ambulator nu a reușit să obțină o scădere a valorilor tensiunii arteriale sub 150/90 mmHg.

Pe baza rezultatelor obținute considerăm că administrarea metoprololului tartrat în diverse concentrații este indicată la toți bolnavii hipertensivi care nu prezintă contraindicații de administrare a betablocantelor. S-a constatat că administrarea în monoterapie are eficiență maximă la bolnavii tineri și la bolnavii recent depistați cu sau fără terapie hipotensoare cu condiția ca vechimea maximă a tratamentului să fie de 4-5 ani și ca bolnavul să nu fi beneficiat anterior de betablocante. Persoanele în vârstă, vechi hipertensivi, cu prezența comorbidităților sau a complicațiilor HTA, necesită în peste 80% din cazuri asociere medicamentoasă, excluzându-se medicația folosită în tratamentul comorbidităților sau a complicațiilor. În ceea ce privește relația cost eficiență putem acorda calificativul maxim medicamentului descris (atât din punct de vedere al costului cât și din punct de vedere al ușurinței administrării acestuia).

Keywords: metoprolol tartrate, arterial hypertension, diabetes mellitus, quality of life

Introduction

Betablockers are still amongst the most important pharmaceutical agents to initiate or continue an antihypertensive treatment. The official position of the 2007 guidelines on the treatment of hypertension (HT) is different from that of the guidelines of the British Society of Hypertension [1,2].

Although in the 2006 guidelines of the British Society of Hypertension betablockers were no longer considered first line antihypertensive agents, the 2007 guidelines of the ESH/ESC (European Society of Hypertension/European Society of Cardiology) note that this class of drugs can still be used in many patients, except in those with modified glucose tolerance or metabolic syndrome, in whom it may increase the risk of diabetes and its complications, especially in combination with a thiazidic diuretic [1,3]. In certain associated conditions such as *angina pectoris*, post-infarction or heart failure, betablocker therapy is even recommended. Betablockers provide cardiovascular protection on multiple levels, reduce blood pressure values similar to other classes of antihypertensive drugs, and have a proven therapeutic role in heart failure [4,5,6].

Selective betablockers have proven their efficiency in three very important areas of the cardiovascular pathology: hypertension, angina and

arrhythmias. The latest selective betablockers have partially resolved the problem of their three major contraindications: *asthma bronchiale*, peripheral arteriopathy and diabetes [6,7].

Betablockers also have the capability to act upon each link of the cardiovascular continuum, as it was elegantly highlighted during the 2008 Congress of the European Society of Cardiology in Munich [7,8].

As far as metoprolol is concerned, it was the first selective antagonist of the beta-1-adrenergic receptors of the heart. It was demonstrated that if it is administered in the first 24 hours following a myocardial infarction, it reduces mortality, the risk of reinfarction and the appearance of residual angina in the post-infarction period [9]. Comparative studies have demonstrated that its efficiency is superior to non-selective betablockers, but also to hydrophil betablockers such as atenolol or sotalol (by modulating the hydrophil/lipophil ratio, and achieving a high penetration rate through the blood-brain barrier) [10,11,12]. However, its metabolism is CYP2D6-dependent; poor metabolizers develop more frequently side effects (e.g. severe bradycardia) [13].

Administration of metoprolol in patients with left ventricular dysfunction resulted in an increased ejection fraction of the left ventricle, a longer diastolic relaxation period and an improved effort capacity, especially in patients with ischemic dilatative cardiomyopathy, with an improvement in the patient's NYHA (New York Heart Association) stage. The advantage of its negative chronotropic effect is a longer ventricular filling, which also reduces the myocardium's need of oxygen [14,15].

Regarding the advantages of administering metoprolol to hypertensive patients, it has been noted that besides lowering blood pressure values, metoprolol reduces the incidence of cerebrovascular events, silent ischemic episodes and sudden cardiac death. Another advantage of metoprolol treatment in hypertensive patients is the lack of postural hypotension. As a monotherapy, it is recommended to patients with mild or moderate hypertension. Studies investigating the administration of a single dose of 50, 100 or 200 mg of metoprolol tartrate have shown that in 38% of patients receiving an initial dose of 50 mg the dose had to be doubled to 100 mg because of the insignificant changes in blood pressure values. After 12 weeks of treatment diastolic values decreased below 95 mmHg in 69% of patients, only 15-17% of them needing a dose of 200 mg of metoprolol tartrate. Administration of two doses, 2 x 50 mg or 2 x 100 mg metoprolol tartrate reduced diastolic values below 95 mmHg in 74% of the patients, after 12 weeks of treatment [7,16].

The aim of the present study was to evaluate the efficiency of metoprolol tartrate of various concentrations in the treatment of patients with diverse forms of hypertension - pure, with comorbidities and/or complications, in the absence of contraindications for the use of betablockers.

Materials and Methods

The study was performed at the 3rd Medical Clinic - Cardiology of Târgu Mureș, between June 1st. 2009 - September 1st. 2010, involving a group of 200 patients, 128 men (64%) and 72 women (36%), with an average age of $51,7 \pm 7,2$ years (32-77 years), diagnosed with hypertension (HT), without prior antihypertensive medication - 116 patients (58%), or with old hypertension (1-15 years at the moment of diagnosis) and various ambulatory therapeutic schemes of questionable efficiency - 84 patients (42%), in which the ambulatory treatment could not lower blood pressure values below 150/90 mmHg. The study group was divided into 4 groups:

- Group 1 – 50 patients with pure HT;
- Group 2 – 50 patients with HT and type 2 diabetes, controlled with oral antidiabetic medication;
- Group 3 – 50 patients with HT and coronary heart disease (CHD);
- Group 4 – 50 patients with HT and various stages of heart failure.

The Târgu-Mures University of Medicine and Pharmacy's ethic committee has granted the approval for the current study, also written approvals from patients were obtained.

Selection criteria:

- Patients diagnosed with essential arterial hypertension without causes of secondary arterial hypertension
- Inefficient or inexistent ambulatory or hospital antihypertensive treatment
- Absence of treatment with metoprolol tartrate or inefficient treatment with other betablockers
- Absence of contraindications for the use of betablockers
- Cooperative patients who are actively participating in the study

Description of the studied group according to the protocol

Risk factors taken in consideration, and the number of patients with these risk factors in all 4 groups are presented in the table below.

Table I
Risk factors

Risk factor	Gr. 1 (50 patients)	Gr. 2 (49 patients)	Gr. 3 (50 patients)	Gr. 4 (48 patients)
Excess weight (kg)	34	37	28	29
Alcohol consumption	12	10	9	17
Smoking	27	24	36	25
High sodium intake	27	34	31	42
High lipid intake	22	32	35	28
Maximum values of SBP	178 ± 17 mmHg	198 ± 12 mmHg	189 ± 15 mmHg	168 ± 19 mmHg*
Maximum values of DBP	105 ± 7 mmHg	102 ± 13 mmHg	109 ± 7 mmHg	97 ± 11 mmHg
Age of HT (years)	6.3 ± 2.7	7.1 ± 1.6	5.9 ± 2.3	10.5 ± 2.1

*maximum blood pressure values from the patient's history (208±19 /107±17 mm Hg); SBP = Systolic blood pressure; DBP = diastolic blood pressure.

Regarding the excess weight and maximum values of SBP, the highest number of patients was in the second group of patients (with HT and type 2 diabetes), while smoker patients and patients with the highest numbers of years of HT were more frequent in the 3rd group (with HT and CHD)

Table II
Antihypertensive medication prior to the study

	Gr. 1 (50 patients)	Gr. 2 (49 patients)	Gr. 3 (50 patients)	Gr. 4 (48 patients)
ACE inhibitors	17	14	26	24
Betablockers	5	1	17	9
Calcium channels blockers	12	11	13	8
Diuretics	18	13	12	22
Sartans	12	15	8	7
Other	7	5	8	3

ACE = Angiotensin converting enzyme;

Most of the patients prior to the study were on ACE inhibitors (81 of them, most of them in the 3rd group) and diuretics (65 of them, most in the 4th group).

Table III
Associations of drugs at the end of study

	Gr. 1 (50 patients)	Gr. 2 (49 patients)	Gr. 3 (50 patients)	Gr. 4 (48 patients)
ACE inhibitors	12	18	24	17
Calcium channels blockers	10	15	19	10
Diuretics	13	10	11	16
Sartans	12	17	14	10
Hypolipidemic drugs	5	11	18	9

At the end of the study most of them were on ACE inhibitors as well (71 of them, most in the 3rd group) and Ca²⁺ blockers (54 of them, most in the 3rd group)

Protocol description

I. Initial evaluation (upon inclusion into the study)

* Demographic data

- * Anamnestic data
- * Physical examination
- * Paraclinic explorations
- * Questionnaire regarding the quality of life

II. Visit 1 (at 2 weeks)

III. Visit 2 (at 2 months)

IV. Visit 3 (at 4 months)

V. Visit 4 (at 8 months)

VI. Visit 5, final (at 12 months)

- * Final therapeutic scheme
- * Questionnaire regarding the quality of life
- * End Point tolerance to medication

After 2 weeks of treatment 3 patients (1.5%) belonging to group 2 and 4 were excluded from the study, 1 patient (0.5% of the total, 2% of the group) accused the pronounced coldness of the limbs and refused further collaboration; 2 patients from the group with HT and heart failure (1% of the total, 4% of the group) presented pronounced bradycardia with a heart rate under 45/min, and betablocker therapy was stopped.

The final study group had the following configuration:

- Total number of patients whose data was analyzed - 197
- Group 1 – 50 patients with pure arterial hypertension;
- Group 2 – 49 patients with HT and type 2 diabetes, controlled with oral antidiabetic medication;
- Group 3 – 50 patients with HT and coronary heart disease (CHD);
- Group 4 – 48 patients with HT and various stages of heart failure.

The entire group was monitored with ambulatory blood pressure monitoring (ABPM) before starting the study, and average blood pressure values over 24 hours were taken into consideration. Also, blood pressure values reported at the end of the study were average values obtained through 24 hour ABPM.

Results and Discussion

Data analysis was performed with the Epi Info software; Mann-Whitney test, Chi square, 2 tailed p and Fishers exact test, with a confidence limit of 95% were used. A p value of <0.05 was considered statistically significant.

Continuous variables are reported as mean $\pm$ standard deviation (SD) and categorical variables as observed number of patients.

Table IV
Biological modifications at the beginning and at the end of study

	Gr. 1 (50 patients)	Gr. 2 (49 patients)	Gr. 3 (50 patients)	Gr. 4 (48 patients)
Initial vs. Final serum cholesterol (mmol/L)	5.6 $\pm$ 1.7 vs. 5.5 $\pm$ 1.4	5.9 $\pm$ 1.6 vs. 5.4 $\pm$ 1.8	6.1 $\pm$ 2.1 vs. 6.0 $\pm$ 1.9	5.5 $\pm$ 1.3 vs. 5.2 $\pm$ 1.3
p value for serum cholesterol	0.0786	0.1513	0.0837	0.1218
Initial vs. Final triglycerids (mmol/L)	1.8 $\pm$ 0.96 vs. 1.7 $\pm$ 0.9	1.8 $\pm$ 0.8 vs. 1.8 $\pm$ 0.6	1.9 $\pm$ 1.0 vs. 1.7 $\pm$ 1.1	1.6 $\pm$ 0.8 vs. 1.6 $\pm$ 0.9
Initial vs. final HDL-cholesterol (mmol/L)	1.45 $\pm$ 0.12 vs. 1.48 $\pm$ 0.13	1.37 $\pm$ 0.2 vs. 1.43 $\pm$ 0.29	1.2 $\pm$ 0.75 vs. 1.41 $\pm$ 0.66	1.3 $\pm$ 0.14 vs. 1.33 $\pm$ 0.21
Initial vs. final LDL-cholesterol (mmol/L)	3.1 $\pm$ 0.6 vs. 3 $\pm$ 0.7	3.6 $\pm$ 0.8 vs. 3.4 $\pm$ 1.2	3.4 $\pm$ 1.1 vs. 2.7 $\pm$ 0.9	3.2 $\pm$ 0.7 vs. 3.3 $\pm$ 0.8
Initial vs. Final Glycemia (mmol/L)	5.6 $\pm$ 0.9 vs. 5.4 $\pm$ 0.7	6.2 $\pm$ 2.9 vs. 6.1 $\pm$ 2.6	5.6 $\pm$ 0.8 vs. 5.8 $\pm$ 1.1	5.4 $\pm$ 0.5 vs. 5.6 $\pm$ 0.8
p value for glycemia	0.1153	0.1313	0.0689	0.0747

HDL = high density lipoproteins; LDL = low density lipoproteins.

These modifications of the examined biological parameters are not statistically significant (p > 0.05), demonstrating the neutral effect of metoprolol on the metabolism of the studied group.

Table V

Echocardiographic characteristics at the beginning and at the end of study

	Gr. 1 (50 patients)	Gr. 2 (49 patients)	Gr. 3 (50 patients)	Gr. 4 (48 patients)
Initial vs. Final LVEF (%)	62 ± 11 vs. 66 ± 10	65 ± 10 vs. 66 ± 12	64 ± 13 vs. 66 ± 14	52 ± 9 vs. 59 ± 12
Initial vs. Final diastolic dysfunction of the LV (%)	16 vs. 9	23 vs. 12	19 vs. 12	35 vs. 23
Initial and Final LVH	15	16	12	32
Initial and Final dilatation of the LV	6	7	7	13

LVEF = left ventricular ejection fraction; LV = left ventricle.

The echocardiographic examination shows the improvement of the left ventricular pump function in all groups, with a lower number of patients with diastolic dysfunction of the left ventricle, and a statistically significant increase of the left ventricular ejection fraction ($62 \pm 11\%$ vs. $66 \pm 10\%$ in group 1, $p < 0.001$). In a small number of patients the diastolic relaxation disorders persisted (12%-27% depending on the group).

Table VI

Questionnaire regarding the evolution of the quality of life and associated symptoms at the beginning and at the end of study

	Gr. 1 (50 patients)	Gr. 2 (49 patients)	Gr. 3 (50 patients)	Gr. 4 (48 patients)
Initial vs. Final quality of life	22 vs. 5	27 vs. 12	19 vs. 6	43 vs. 13
Initial vs. Final working capacity	20 vs. 3	22 vs. 13	25 vs. 8	45 vs. 22
Initial vs. Final sexual activity	6 vs. 8	12 vs. 15	10 vs. 15	28 vs. 32
Initial vs. Final digestive symptoms	11 vs. 8	18 vs. 15	15 vs. 14	17 vs. 14
Initial vs. Final respiratory symptoms	6 vs. 5	5 vs. 5	9 vs. 8	24 vs. 13
Initial vs. Final neurological symptoms	26 vs. 14	28 vs. 21	17 vs. 9	42 vs. 23

As far as the improvement in the quality of life of patients is concerned, we observed a statistically significant improvement of symptoms ($p = 0.035$ for quality of life, $p = 0.002$ for working capacity, $p = 0.413$ for

sexual activity, $p = 0.355$ for respiratory symptoms, $p = 0.0017$ for neurological symptoms), the only negative aspect being the worsening of the quality of sexual activity, due to the erectile dysfunction induced by the betablocker treatment.

Table VII
Evolution of heart rate during the study (heart beats/ minute)

	Gr. 1 (50 patients)	Gr. 2 (49 patients)	Gr. 3 (50 patients)	Gr. 4 (48 patients)
Initial evaluation	77 ± 12	72 ± 17	80 ± 21	83 ± 24
Visit I	70 ± 10	70 ± 12	77 ± 13	75 ± 13
Visit II	65 ± 13	67 ± 9	70 ± 12	69 ± 12
Visit III	64 ± 5	63 ± 10	63 ± 9	66 ± 10
Visit IV	63 ± 11	62 ± 15	62 ± 17	65 ± 18
Visit V	58 ± 13	60 ± 7	61 ± 14	60 ± 15
Final evaluation	58 ± 13	60 ± 7	61 ± 14	60 ± 15

We noted a tendency to bradycardia in all groups, the decrease of heart rate being highly statistically significant ($p < 0.001$) in the entire studied group (197 patients), and also for each group separately.

Table VIII
Doses of metoprolol during the study (no. of patients)

		Gr. 1 (50 patients)	Gr. 2 (49 patients)	Gr. 3 (50 patients)	Gr. 4 (48 patients)
Treatment initiation	2 x 25 mg	12	20	15	18
	2 x 50 mg	34	28	31	29
	2 x 100 mg	4	1	4	1
Visit I	2 x 25 mg	10	19	14	16
	2 x 50 mg	33	29	30	31
	2 x 100 mg	7	1	6	1
Visit II	2 x 25 mg	10	19	13	15
	2 x 50 mg	32	30	30	31
	2 x 100 mg	8	0	7	2
Visit III	2 x 25 mg	10	18	12	15
	2 x 50 mg	32	31	31	30
	2 x 100 mg	8	0	7	3
Visit IV	2 x 25 mg	9	18	10	14
	2 x 50 mg	32	31	33	31
	2 x 100 mg	9	0	7	3
Visit V	2 x 25 mg	9	18	10	13
	2 x 50 mg	33	31	33	32
	2 x 100 mg	8	0	7	3
Final dose	2 x 25 mg	9	18	10	13
	2 x 50 mg	32	31	33	32
	2 x 100 mg	8	0	7	3

Regarding the doses necessary to obtain the target blood pressure values of our study, they are in accordance with the large trials, the most frequently used dose being 2 x 50 mg, in more than 60% of the patients.

Table IX
Evolution of blood pressure values during the study (mmHg)

		Gr. 1 (50 patients)	Gr. 2 (49 patients)	Gr. 3 (50 patients)	Gr. 4 (48 patients)
Initial evaluation	SBP mmHg	178 ± 17	198 ± 12	189 ± 15	168 ± 19
	DBP mmHg	105 ± 7	102 ± 13	109 ± 7	97 ± 11
Visit I	SBP mmHg	158 ± 14	157 ± 13	165 ± 12	160 ± 17
	DBP mmHg	99 ± 11	97 ± 12	100 ± 13	93 ± 10
Visit II	SBP mmHg	151 ± 12	148 ± 12	145 ± 11	144 ± 9
	DBP mmHg	93 ± 9	93 ± 11	95 ± 10	91 ± 11
Visit III	SBP mmHg	132 ± 17	131 ± 14	140 ± 9	138 ± 8
	DBP mmHg	89 ± 8	85 ± 9	90 ± 9	87 ± 10
Visit IV	SBP mmHg	131 ± 15	128 ± 11	133 ± 13	134 ± 13
	DBP mmHg	85 ± 7	84 ± 8	89 ± 8	85 ± 11
Visit V	SBP mmHg	128 ± 12	123 ± 10	130 ± 11	131 ± 10
	DBP mmHg	84 ± 9	78 ± 9	88 ± 6	77 ± 10
Final evaluation	SBP mmHg	128 ± 12	123 ± 10	130 ± 11	131 ± 10
	DBP mmHg	84 ± 9	78 ± 9	88 ± 6	77 ± 10
p value (initial vs. final)		p<0.0001	p<0.0001	p<0.0001	p<0.0001

Our study has reached its PRIMARY END-POINT, the blood pressure values decreased in each studied group, with a statistically significant ($p < 0.0001$) decrease in the entire group, and the target values specified in the guidelines were achieved.

The **efficiency of the studied drug was 100%** in the entire group, blood pressure values decreasing below 140/90 mmHg, the percentage of patients needing drug associations being under 50%.

The end-point of tolerance was very good. With the exception of the 3 patients excluded from the study, metoprolol was tolerated very well by the patients, and we consider that we have also reached our secondary end-point, by improving their quality of life (with the exception of sexual activity).

Conclusions

Based on our results we consider that the administration of metoprolol Tartrate in various concentrations is indicated in all hypertensive patients in the absence of contraindications for the use of betablockers.

Our study concluded that monotherapy is efficient mainly in young patients and patients with recently diagnosed HT with or without treatment, provided the treatment is maximum 4-5 years old, and the patient has not been given betablockers before.

Older patients, with comorbidities or HT related complications need an association of drugs in 80% of cases, excluding the medication used in the treatment of comorbidities or complications.

The study concludes that the average dose of metoprolol is lower in diabetic patients than in other groups, drug association being preferred in these cases, to avoid the risk of hypoglycemia and the masking of its signs of sympathetic stimulation.

Patients with comorbidities and complications need drug associations more frequently than patients with pure hypertension, given their parallel clinical conditions.

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