© Military Pharmacy and Medicine • 2012 • 1 • 8 – 14

β- blockers and diabetes mellitus

Jacek Owczarek[1], Anna Wiktorowska-Owczarek[2]

[1] Biopharmaceutical Department, Chair of Biopharmacy of Medical University of Lodz, Poland
[2] Pharmacology Department, Chair of Pharmacology and Clinical Pharmacology of Medical University of Lodz, Poland

Author's address:
Jacek Owczarek, Biopharmaceutical Department, Chair of Biopharmacy of Medical University of Lodz, ul. Muszyńskiego 1, 90-151 Łódź, Poland; phone: (+48) 677 91 22, e–mail: jacek.owczarek@umed.lodz.pl

Received: 2012.02.11 • **Accepted:** 2012.03.01 • **Published:** 2012.03.27

Summary:

During the 50 years since the discovery of propranolol, β-blockers established their position on the grounds of numerous clinical trials on treatment of coronary artery disease, hypertension and heart failure. Absolute contraindications greatly limit effective treatment and unfavorable metabolic profile is often the cause of discontinuation of treatment. Epidemiological data indicate a significant rise in a population of patients suffering from diabetes and cardiovascular diseases. A particular conflict occurs between those disorders, namely – β-blockers, leading to a reduced β-blocker administration in diabetic patients. In this article, we present the role of β-blockers in selected cardiovascular disorders with coexistent diabetes as well as positive features of this group of drugs despite some of their disadvantages.

Key words: β-blockers, cardiovascular diseases, diabetes mellitus.

Introduction

Diabetes mellitus is a chronic metabolic disease characterized by elevated blood glucose concentration (hyperglycemia) as a result of dysfunction of pancreatic Langerhans' islet beta cells and/or peripheral cellular insulin resistance (organism is not able to utilize insulin effectively). Persistent hyperglycemia as well as disorders of fat and protein metabolism lead to development of acute complications (coma) or chronic organ and systemic damage. Vascular complications of diabetes lead to increased risk of arterial hypertension, cardiac ischemic disease and heart failure. Diabetes significantly elevates the risk of acute cardiovascular events (myocardial infarction, stroke) [1,2]. Multidirectional actions for primary and secondary prevention of acute cardiovascular events, based on clinical and laboratory research, involve the use of β_1-blockers. However, most of them promote weight gain and exert an adverse influence on lipid metabolism. Interference of agents blocking β-adrenergic receptors with sympathetic nervous system activity may be the reason for the alleviation of symptoms of hypoglycemia. This is a consequence of inadequate administration of medicines in relation to the nutritional supply and intensity of physical exercise. Symptoms of hypoglycemia include: excessive sweating, palpitations, and tremor.

They are caused by autonomic nervous system stimulation. Patients may also experience nausea and headaches. With significant hypoglycemia (usually < 55mg%), the following symptoms occur: confusion, somnolence, impaired motor coordination, blurred vision and, at last, coma. Episode of severe hypoglycemia always requires immediate medical intervention [3]. One of the cohort studies revealed significant differences

between groups of patients treated with selective vs. non-selective β-blockers. It was confirmed that patients treated with insulin are exposed to greater risk of hypoglycemia in case of simultaneous use of non-selective β-blockers. However, that did not apply to patients treated with β_1-blockers [4]. High prevalence of diabetes and co-existence of cardiovascular complications are common causes of β-blocker administration. However, numerous contraindications often lead to a conviction that there are major or even absolute contraindications for their use in patients with diabetes. In this article, authors attempt to present current information on the significance of β_1-blocker use in patients with coexistent cardiovascular disease and diabetes.

β-blockers

Discovery and development of β-adrenergic receptor antagonists (β_1-blockers) may be considered one of the most important advances and breakthroughs in the history of cardiovascular pharmacology. The first β-blocker – propranolol – was discovered in 1964 by Sir James W. Black (Scottish doctor and a pharmacologist living in the years 1924-2010), who received the Nobel Prize in the field of physiology and medicine for it in 1988. During those times, the majority of research studies focused on seeking medicines increasing supply of oxygen to the heart. However, Sir James asked himself an opposite question: "Could the myocardial need for oxygen be reduced?"

It turned out to be possible thanks to introduction of β-blockers. A 4-fold reduction in mortality in comparison to a group not receiving this drug was observed after only the first three years following introduction of propranolol onto the market [5].

Beta-adrenolytics inhibit two types of β-adrenergic receptors: β_1 and β_2 to various extent. This group is characterized by great pharmacokinetic and pharmacodynamic heterogeneity. Differences in pharmacodynamics are related to β_1/β_2-selectivity, intrinsic sympathomimetic activity and vasodilatatory capacity (Table 1). Cardioselective β-blockers (they only inhibit β_1) are superior to non-selective ones due to the reduction of adverse events associated with β_2 blockade. Intrinsic sympathomimetic activity is characterized by weak β_1 stimulation with simultaneous basic antagonism of those receptors and is exhibited by acebutolol and, above all, pindolol [6,7].

Table 1: The division of β-blockers using in cardio-vascular diseases

I generation Non-selective β-blockers	II generation β1-selective blockers	III generation	
		Non-selective β-blockers with additional actions	β1-selective blockers with additional actions
Propranolol Pindolol	Acebutolol Atenolol Bisoprolol Metoprolol	Carvedilol Labetolol	Celiprolol Nebivolol

New, so-called III-generation β –blockers were introduced in the past few years. They differ from older preparations by additional characteristics such as ability to block α1-adrenergic receptors (carvedilol, labetalol), stimulate NO release (nebivolol), β_2-receptor antagonism (celiprolol), inhibition of calcium ion influx (carvedilol, betaxolol), and antioxidative properties (carvedilol) [6, 8, 9].

Pharmacokinetic differences between β-blockers concern their lipophilicity. Propranolol exhibits its greatest affinity to lipids, while metoprolol, carvedilol and betaxolol – moderate. Strong lipophilic properties result in a good blood-brain barrier penetration, which may cause sympathetic nervous system suppression [6,7].

Basic contraindications for β-blockers include: poorly-controlled asthma, II and III degree atrioventricular block, sick sinus syndrome and sinus bradycardia < 50 beats/minute during arousal – especially if it is symptomatic (Morgagni-Adams-Strokes syndrome, MAS). The data available in the literature indicate that β-adrenolytic agents promote weight gain [10], exert an unfavorable influence on lipid metabolism and increase (in comparison to other drugs) the incidence of diabetes [11,12]. They may also "mask" the symptoms of hypoglycemia.

Treatment with β-blockers in ischemic heart disease

The first studies conducted by Sir James were already directed at treating angina pectoris through blocking the influx of endogenous catecholamines (epinephrine and norepinephrine)

to the heart, decreasing heart rate and contractility and therefore, reducing oxygen consumption. Therapy with β-blockers lowers the demand of cardiac muscle for oxygen at rest and, above all, during stress, physical exercise and in situations associated with stimulation of sympathetic nervous system [13]. The remaining mechanisms of β-blockers playing a positive role in ischemic heart diseases are presented in Table 2.

Table 2: The properties of β-blockers predisposing them to use in angina pectoris

Angina pectoris
▸ Reduction heart rate and contractility
▸ Decrease oxygen demand
▸ Decrease peripheral vascular resistance in long-term administration
▸ Lowering blood pressure
▸ Reduction afterload

Acute coronary syndromes such as unstable angina and myocardial infarction occur in diabetics very often [14-16]. Clinical studies, including metaanalyses, proved significant benefits associated with β_1-blocker use in patients after myocardial infarction [17]. These benefits include reduction in overall mortality by about 23% [18], risk of recurrent MI and death due to cardiac causes. Diabetic patients gain particular benefits from the use of β_1-blockers, as demonstrated through a reduction of mortality in patients following myocardial infarction and decrease in the number of patients with newly diagnosed myocardial infarction [19-24]. Therefore, β-blockers are particularly indicated in all diabetic patients with acute coronary syndromes [19,20,25].

It is important to individually select a proper drug from this group taking into consideration co-morbidities and type of treatment for diabetes. Selective β_1-blockers should be preferred in patients receiving insulin while administration of α-1 and β-adrenergic receptor blockers such as carvedilol may bring additional benefits in patients with co-existent peripheral artery disease or substantial insulin resistance [26].

However, as current data show, diabetics suffering from ischemic heart disease are often deprived of this life-saving treatment [27-29], which may result from established beliefs regarding detrimental influence of β-blockers in this group of patients.

Treatment with β-blockers in arterial hypertension

In the year (1965) following introduction of propranolol to the market, Prichard and Gillam demonstrated effectiveness of this drug in the treatment of hypertension [30]. Properties of β-blockers that determine their use in hypertension are presented in Table 3.

Table 3: Mechanism of hypotension action of β-blockers

Hypotension effects of β-blockers – mechanism of action
▸ Decrease cardiac output
▸ Inhibition of RAA system via inhibition renin release
▸ Blockade presynaptic β-adrenoceptors and inhibition of Norepinephrine release
▸ Decrease central actions
▸ Decrease peripheral vascular resistance in long-term administration
Additional hypotension effects of III generation of β-blockers – mechanism of action
▸ Production of nitric oxide –nebivolol
▸ Blockade of α_1-adrenoreceptors – carvedilol
▸ Activation of β_2-adrenoceptors – celiprolol
▸ Blockade of Ca^+ entry – carvedilol, betaxolol

Among the most important characteristics of this group of drugs we should mention: reduction in cardiac output, inhibition of renin release by juxtaglomerular cells and therefore, inhibition of RAA system (rennin-angiotensin-aldosterone), as well as blocking presynaptic β-adrenergic receptors, thus inhibiting norepinephrine release. Reduction in peripheral vascular resistance occurs in effect of long-term β-blocker administration. On the other hand, III generation β-blockers possess additional hypotensive properties such as nitrous oxide production, blockage of α1-adrenergic receptors, activation of β2-adrenergic receptors and inhibition of calcium ion influx [6,9]. This allows for broadening the indications for their use.

Beta-blockers, next to diuretics, calcium channel blockers, ACE inhibitors and angiotensin receptor blockers constitute one of five classes

of hypotensive drugs that, according to ACCF/AHA 2011 (American College of Cardiology Foundation/American Heart Association), significantly reduce the risk of cardiovascular events and are indicated during initiation as well as continuation of hypotensive treatment both in monotherapy and in combination. Particular attention should be paid to careful administration of β-blockers, or even their avoidance, in therapy of patients with metabolic syndrome or at risk of diabetes, especially when they are used in combination with thiazide diuretics. Nevertheless, experts' views on the choice of hypotensive therapy consider preferential use of β-blockers in patients after myocardial infarction, with angina pectoris, for rate control in permanent atrial fibrillation, in heart failure and during pregnancy.

Two recent large clinical studies [31,32] and one metaanalysis [33] demonstrated that β-blockers, especially atenolol [9], are less effective in stroke prevention, although they reduce the risk of coronary incidents and mortality equally well to other drugs. There were benefits associated with use of β –blockers in patients with angina pectoris, heart failure and after recent MI [18,34,35]. Therefore, β-blockers may be considered during both initiation as well as continuation of hypotensive treatment. In this group of patients, special attention should be paid to β-blockers exerting vasodilatatory effects. These include carvedilol and nebivolol, which cause less pronounced metabolic disturbances or are completely devoid of this effect [36].

Therapy with β-blockers in heart failure

Heart failure of various etiologies significantly worsens the quality of life and is a cause of frequent hospitalizations. Research studies confirming the benefits associated with administration of beta-adrenergic receptor blocking drugs, despite their negative inotropic effects, were taken into account in the recommendations. Current guidelines of the European Society of Cardiology recommend using blockers of β-adrenergic receptors in all patients with symptomatic heart failure and left ventricular ejection fraction (LVEF) of ≤ 40%. Benefits associated with their use in heart failure patients include, among other things, reduction in the number of hospitalizations due to exacerbation of heart failure and, most importantly, improvement in survival and quality of life [37,38].

As a consequence of numerous trials, including CIBIS II (with bisoprolol), MERIT-HF (with metoprolol), SENIORS (with nebivolol) and COPERNICUS (with carvedilol), several β-blockers - carvedilol, bisoprolol, metoprolol and nebivolol - were approved for treatment of chronic, stable heart failure (NYHA II-IV) [7,8].

Following introduction of propranolol by Sir James, heart failure was a contraindication to its use together with several other drugs from this group. Frankly, their administration seemed counterintuitive. However, cardiac function impairment due to chronic sympathetic nervous system activation pointed to a new direction in treatment – β-blockers. They counteract the structural changes in the heart and vessels, myocyte damage and, as follows, decrease in contractility, reduction in concentration of β_1-adrenergic receptors, increased cytokine levels, apoptosis, ischemia and other factors (Table 4) resulting from sympathetic nervous system overactivity.

Properties of β-blockers and clinical trials provided the grounds for current guidelines developed by American Heart Association and American College of Cardiology (AHA/ACC) stating that this group of drugs should be used in all patients with symptomatic LV systolic dysfunction. Heterogeneity of β-blockers is also apparent in their administration in heart failure. Metoprolol and bisoprolol are β_1-selective, as is nebivolol, which additionally possesses vasodilatory properties, while carvedilol is a β_1-, β_2- and α_1-adrenoreceptor antagonist exhibiting anti-oxidant, anti-apoptotic and anti-endothelin effects. Despite those differences, all drugs reduced mortality by about 34% in above mentioned clinical trials [7,8].

Conclusions

Progress in pharmacotherapy of cardiovascular diseases is the reason for increase in the number of indications for treatment with β-adrenergic receptor blockers. Despite disadvantages and contraindications for β-blockers, clinical trials

Table 4: Mechanism of hypotension action of β-blockers*

The international name	The trade name and doses	Indications
Acebutololum	Sectral 200 and 400 mg	A, H, IHD
Atenololum	Atenolol Sanofi 25 and 50 mg	A, H, IHD, MI
Bisoprololum	Bisoratio 5 and 10 mg	HF, H, IHD
	Coronal 5 and 10 mg	H, IHD
Carwedilolum	Atram 6,25; 12,5; 25 mg	HF, H, IHD
	Avedol 3,125; 6,25; 12,5; 25 mg	HF, H, IHD
	Carvetrend 3,125; 6,25; 12,5; 25 mg	HF, H, IHD
	Carvedigamma 6,25; 12,5; 25 mg	HF, H, IHD
	Carvedilol Teva 6,25; 12,5; 25 mg	HF, H, IHD
	Carvedilol-ratiopharm 6,25; 12,5; 25 mg	HF, H, IHD
	Coryol 3,125; 6,25; 12,5; 25 mg	HF, H, IHD
	Dilatrend 6,25; 25 mg	HF, H, IHD, LVEF
	Hypoten 6,25; 12,5; 25 mg	HF, H, IHD
	Symtrend 3,125; 6,25; 12,5; 25 mg	HF, H, IHD
	Vivacor 6,25; 12,5; 25 mg	HF, H, IHD
Metoprololum	Metocard 50 and 100 mg	A, H, IHD, T
Propranololum	Propranolol WZF 10 and 40 mg	A, Ax, CH, ET, H, IHD, M, P, PH, T

*
The Table was based on Summaries of Product Characteristics published on the website of the Ministry of Health (leki.urpl.gov.pl/index.php) included in a Declaration of the Minister of Health, of 27 February 2012 on the list of reimbursed medicinal products and foods for special medical purposes valid as of 1March 2012 (Official Journal of Minister of Health of 27 February 2012, item 4).

Ax – anxiety,
A-arrhythmias,
CH –cardiomyopathy hyperthrophic,
ET – essential tremor, HF – heart failure,
H – hypertension,
IHD – ischaemic heart disease,
LVEF –left ventricular ejection fraction ≤ 40% after MI,
M – migraine,
MI –myocardial infarction,
P – phaeochromocytoma,
PH – portal hypertension,
T - thyrotoxicosis

and broadly-defined benefits such as reduced hospitalization rates and mortality argue for their application in ischemic heart disease, arterial hypertension and heart failure. Co-existence of diabetes, which leads many doctors to avoid β-blockers, should not be the grounds for not using these drugs in those patients. It should be noted that clinical benefits ensuing from application of β_1-blockers in diabetic patients with heart failure and/or after myocardial infarction are undisputable and these patients should not be deprived of treatment with those drugs.

This group of drugs should not be the first choice for patients with arterial hypertension. However, diabetes and pre-diabetic state are not absolute contraindications to such treatment. Moreover, the variety of characteristics, especially among III generation β-blockers, allows for selection of an appropriate medication for patients with diabetes. Table 5 presents all drugs that were registered and refunded in Poland (not all of III generation drugs appeared

in this table because of that) with their indications based on the summaries of product characteristics. Indications, as shown in the table, may differ between products with the same international name.

Acknowledgments:

Article funded by Medical University of Lodz within the statutory activity (503/1-023-01/503-01 and 503/3-011-02/503-01).

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40. Ax – anxiety, A-arrhythmias, CH –cardiomyopathy hyperthrophic, ET – essential tremor, HF – heart failure, H – hypertension, IHD – ischaemic heart disease, LVEF –left ventricular ejection fraction ≤ 40% after MI, M – migraine, MI –myocardial infarction, P – phaeochromocytoma, PH – portal hypertension, T - thyrotoxicosis