Therapeutic uses of beta-blockers: an update

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Abstract

Beta-blockers play an important role in the treatment of cardiovascular diseases. They constitute a large group of fairly complex agents. They have a wide range of uses, and new indications have also evolved for new and old agents.

We began by reviewing the main pharmacological and pharmacokinetic characteristics of beta-blockers, with particular emphasis on clinically important basic pharmacological differences: potency, structure-activity relationships, membrane stabilizing activity, selectivity, intrinsic sympathomimetic activity, alpha-adrenergic blocking activity, and the variability of the dose--therapeutic ratio of these drugs.

The therapeutic indications for each condition were reviewed, highlighting the beneficial effects of beta-blockers in survivors of myocardial infarction, the efficacy of these agents in the treatment of hypertension, and the promising use of sotalol – a class III drug – in the treatment of cardiac arrhythmias. The experimental uses of beta-blockers in the treatment of dilated cardiomyopathy are also promising.

Finally, the adverse effects and contraindications of beta--blockers are described, and the controversies surrounding their uses in patients with diabetes mellitus, peripheral vascular disease and dyslipidemias are discussed.

Key Words: beta-adrenergic blockers, cardiovascular therapeutics.

Introduction

Beta-blockers constitute an important therapeutic group which, after nearly twenty-five years of clinical use, are still of great importance today, representing a field of activity still expanding. Meanwhile, new drugs have been developed, and the use of other, older drugs has been expanded. It is, therefore, a therapeutic class of major importance in the current arsenal of medical treatments.

However there are some reservations concerning their use both in outpatient and emergency medicine. The complexity of developing the drug – ensuring an offer of specific drug characteristics and diverse properties – and the possible side effects of these drugs in various clinical conditions, contribute to this fact. With a predominantly clinical objective, this review describes the most important characteristics and consensual uses of these drugs in the area of cardiological therapy.

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Concepts of physiology and pharmacology

β-*adrenergic receptors*

Beta-blockers are selective drugs that block the beta receptors in each synapse thereby blocking the actions of the sympathetic nervous system, the nerve endings of which release noradrenaline which is responsible for activating the adrenoreceptors in the myocardial cells.[1] These receptors are polypeptides, located on the surface of the cell membrane of the target cell. In the case of catecholamines, they form a hormone-receptor complex which, through chemical mediation, will stimulate or inhibit several metabolic processes. Antagonists are drugs that interact with receptors and prevent the action of agonists, and agonists are natural or pharmacological agents that interact with a receptor and mimic the normal catecholamine response.[2]

The receptors are dynamic, and the sensitivity of various tissues may depend on their concentration in the tissues. For example, an increase in the number of beta receptors, causing hypersensitivity to agonists, may be caused by chronic exposure to antagonists, a fact with important clinical consequences.[3]

Myocardial adrenergic stimulation leads to an increase in heart rate, contraction strength, and maximum cardiac muscle contraction rate. All these actions involve an increase in cardiac work and a consequent increase in oxygen consumption.[2]

TABLE I

Beta-blockers available in Portugal: main pharmacological characteristics and clinical use

Drug	Trade Name	Selective	ISA	Half-Life	Protein binding (%)	Elimination /Lipid solubility	Initial dose/ nº times per day	IV dose
Atenol	Ancoren, Blokium, Tenormi	yes	no	6-9h	10	Renal only/ –	50 mg/l	5-10 mg
Bisoprol	Concor	yes	no	10-12h	30	renal 50%/ ++	10 mg/l	–
Labetolol	Trandate	no	no	3-4h	85	hepatic 90% ++	100 mg/l	20-50 mg until effective
Metropolol	Lopresor	yes	no	3h	15	mainly hepatic/ +	50-100 mg/2	5-15 mg
Nadolol	Anabet	no	no	16-24h	20	renal only/ –	40 mg/l	–
Penbutolol	Blocotin	no	yes	4-5h	80	hepatic only/ +++	20 mg/l	–
Pindolol	Viskene	no	yes	3-4h	60	hepatic and renal (40%)/ –	5 mg/2	–
Propranolol	Inderal propranolol--rathio	no	no	3-6h	90	hepatic 95% (first passge)/+++	40 mg/3 Inderal LA-160 mg/l	1-10 mg
Sotalol*	Sotacor, darob	no	no	12-15h	5	renal only/ –	80 mg/2	10-20 mg
Tertatolol	Artex	no	no	3h	95	mainly renal /–	5 mg/l	–
Timolol	Blocadren	no	no	4-6h	65	hepatic and renal (20%)/ ±	10 mg/2	0.5-1 mg

*Only available in some central hospitals. To be marketed soon.

Pharmacological differences between beta blockers

Over a hundred beta-blockers have been synthesized, and thirty are now available worldwide for clinical use.[2] *Table I* shows all the agents of this class available in Portugal, with their respective pharmacological characteristics.

Some of these agents have used the division of beta receptors into beta-1 for the heart, and beta-2 for the peripheral circulation and bronchial tree, for the introduction of selectivity. More controversial was the introduction of beta-blockers with associated alpha-antagonism (adrenergic receptors that mediate actions, opposed to betas) or partial agonistic capacity (intrinsic sympathomimetic activity - ISA).

Experimental agents are also attempting to associate the ability to block calcium channels.[2] Other known capabilities are the membrane stabilizing effects ("quinidine-like" – blocking of sodium channels) of some agents, including propranolol.[4]

The pharmacokinetic is not constant throughout the class, and beta-blockers should be divided into two main categories: those which are metabolized by the liver – lipophilic – with relatively short half-lives, and those which are excreted by the kidneys – hydrophilic – with longer half-lives. Another important characteristic affecting the half-life is plasma protein binding.

Propranolol and metoprolol are both liposoluble agents, absorbed by the small intestine and metabolized by the liver. They have a variable bioavailability and relatively short half-lives. Conversely, agents such as nadolol and atenolol are more hydrosoluble and are excreted by the kidneys unchanged. They have a less variable bioavailability in patients with normal renal function.

A prolonged release preparation of propranolol (propranolol coated with insoluble membrane microspheres) was developed, with a longer release curve than that of the usual preparations.[5] On the

other hand, ultra-short-acting beta-blocker preparations have also been developed, such as Esmolol (not yet commercially available in Portugal), which are particularly useful in patients with a higher risk of heart failure. In agents associated with liver metabolism, there is a drastic reduction in serum levels of the circulating drug after the "first passage" through the liver. This explains why much lower doses are needed in intravenous administrations, as they are not subject to this metabolic effect. Bisoprolol, a drug that has recently been investigated, seems to be an agent with balanced (renal and hepatic) excretion and has relatively low protein binding characteristics, leading to high bioavailability.[4,6,7]

Important concepts in clinical practice

Strength (defined by the concentration of agonists necessary to overcome the beta-blocker, with propranolol as standard): it does not have the clinical relevance attributed to it by the pharmaceutical industry, and it is only important to explain the different dosage levels needed for each agent (useful when changing drugs).[2] Clinically, the strength is assessed by the ability to prevent exercise-induced tachycardia.[4,8]

Structure-activity relationships: given that beta-blockers are mostly racemates of optical isomers, it is observed that almost all clinically useful blocking activity is in the negative formula (levorotatory [L] stereoisomer). D-sotalol is different because of its type III Vaughan-Williams antiarrhythmic activity.[9]

Membrane-stabilizing activity: occurs only at doses well above the normal therapeutic dose. There is no evidence that this action is responsible for any negative inotropic effect, since drugs without this capability also depress ventricular function.[10] However, this capability may occur with massive overdoses.[11]

Beta-1 selectivity: refers to the ability to antagonize the sympathomimetic amines in some tissues, at lower doses than in other tissues. It confers the capacity to act on the cardiac receptors, having less influence on bronchial and vascular receptors.[2] However, the beta-1 selectivity is lost at higher doses.

Intrinsic sympathomimetic activity: for beta-1, beta-2 or both. These drugs activate the beta receptor, as well as preventing the access of natural or synthetic catecholamines, and their purpose is to limit the adverse effects of the beta-blockers.

Beta-adrenergic blocking ability: adds a direct, associated vasodilator effect that is particularly useful in limiting the peripheral vascular effects of the beta-blockers. On the other hand, the decrease in peripheral resistance limits the negative action on the cardiac output that is usual in beta-blockers.[2]

Relationship between dose, plasma level and efficacy: the effective dose of a single agent varies from one individual to another, sympathetic tone varies from one individual to another (depending on the circulating catecholamines and beta-receptors present), which involves a more, or less prolonged clinical effect suggested by the pharmacokinetic characteristics. On the other hand, the biological life of beta-blockers may be greater than expected for its plasma half-life, by saturation of the metabolic process and recycling of circulating beta-blockers, or their active metabolites.[2,4]

Therapeutic applications

Despite all the years of clinical experience, there are no studies suggesting that any one beta-blocker, regardless of its properties, has significant advantages over other beta-blockers for the treatment of cardiovascular diseases. When any of the beta-blockers is properly dosed, it may be effective in patients with ischemic heart disease, high blood pressure or arrhythmias.[2,4,7] However, a specific beta-blocker may be more effective in reducing adverse reactions and maximizing the therapeutic effect in specific clinical conditions.[2,4,7] Therefore, for each clinical entity, we sought to present the therapeutic mechanism of the beta-blockers and the agents with which we have more experience, or which present less side effects.

Ischemic heart disease

The three main factors that determine the myocardial oxygen requirements are heart rate, ventricular systolic pressure and left ventricular volume. In fact, the product of heart rate and systolic blood pressure is an important index for determining the threshold angina in a given patient.[1,2,4] Besides the reduction in heart rate, beta-blockers have two favorable outcomes: 1 – lowering blood pressure, thereby reducing the myocardial oxygen requirement, and 2 – a longer diastolic filling time, conditioned by a lower heart rate, which allows an increase in coronary perfusion.[2] Thus, beta-blockers produce an increase in angina-free work capacity in patients with coronary atherosclerosis.[2,4,8]

The capacity to reduce angina attacks led to the

fast-acting outpatient applications. A propranolol spray was developed, which can provide a fast beta blockade and improve exercise tolerance in patients with angor pectoris.[13] Beta-blockers will have less effect when treating ischemia occurring at low heart rates, as in the case of mental stress-induced ischemia.[15] The combined use of beta-blockers with other antianginal therapies proved useful in patients in whom these drugs, alone, are ineffective because besides their intrinsic activity, they block the reflex tachycardia caused by nitrates and calcium antagonists. Similarly, the association between beta-blockers and vasodilator agents is particularly important in patients with angina who have signs of heart failure, decreasing the left ventricular volume, the tension on the myocardial fiber (LaPlace's law) and, consequently, oxygen consumption[2,7] or in patients with possible coronary vasospasm component, which may be potentiated by the antagonism of beta adrenergic receptors.[2,15]

Other therapeutic synergisms have been particularly well studied in relation to calcium channel antagonists. In fact, both drugs produce their antianginal effect by reducing oxygen consumption at clinically relevant effort levels. This reduction is achieved by limiting the level of increase in heart rate and blood pressure that occurs during submaximal exercise. Calcium antagonists achieve this through their vasodilator systemic actions (verapamil and diltiazem also attenuate the increase in heart rate during exercise). On the other hand, both beta-blockers and calcium antagonists prevent the constriction of stenotic epicardial lesions, which normally occur during exercise. Calcium antagonists achieve this by directly dilating the coronary vascular bed, and beta-blockers by altering the regional transtenotic pressure gradients in the vessel perfusing the ischemic region.[15]

Combined therapies, however, should only be used after adjusting the dose up to the maximum dose tolerated by the patient. The combined treatment may be accompanied by an aggravation of side effects, without a corresponding gain in therapeutic efficacy.[15]

Therapy for acute myocardial infarction In the acute phase of infarction, beta-blockers are particularly important for controlling pain, reducing the area of myocardial necrosis, and reducing mortality.[4,16,17] Intravenous forms of metoprolol and atenolol were tested in the hyperacute phase of myocardial infarction, with a reduction in mortality of approximately 15%.[18,19] Metroprolol associated with thrombolysis was evaluated in the TIMI II trial,[20] and also proved to be beneficial for post-infarction angor and re-infarction in the first week after infarction.

In secondary prevention for survivors of myocardial infarction, beta-blockers showed a favorable effect in reducing total and cardiovascular mortality in these survivors, including: sudden death and non-sudden cardiac death, and the incidence of non-fatal infarction (reduction of overall risk of about 25%).[4,16] These favorable results can be explained by their antiarrhythmic and anti-ischemic effects.[2]

It was also proven that clinical trials demonstrating the efficacy of these drugs in improving survival rates of patients with myocardial infarction led to beta-blockers being more frequently prescribed for secondary prevention of coronary events.[21] However, it was demonstrated that insufficient use is made of this class of drugs among the elderly, in patients with heart failure during hospitalization, and even in some patients with angina after infarction.[21]

Instead, in these patients, the use of calcium antagonists was frequent, although studies on their effectiveness for secondary prevention of coronary heart disease have produced negative results[21,22]. The limited use of these drugs among the elderly population appears to be attributable to the fact that the risk of heart failure and bradycardia is greater in these individuals.[21,23] However, beta-blockers save more lives, precisely among the group of patients with heart failure and the elderly.[4,24] In fact, heart failure among the elderly is primarily due to diastolic dysfunction, with systolic function being preserved.[25]

Therapy for angina Beta-blockers are the cornerstone of the treatment for chronic effort-induced angina, for the reasons mentioned. In the treatment of unstable angina, as for acute myocardial infarction, beta-blockers are important in pain control.[2,26] Other associated characteristics, in this clinical situation, include the capacity to reduce the risk of friable atherosclerotic plaque rupture, by reducing the mechanical stress on it[2,26] and, at high concentrations, the capacity to inhibit platelet aggregation.[7,27]

However, these drugs should be avoided if there is any sign of Prinzmetal's angina (conditioned by coronary vasospasm and manifested by transmural ischemia with unstable elevation of the ST-segment); in these cases, the use of calcium antagonists is preferable.[4,28] Silent ischemia (myocardial ischemia that is not associated with anginal pain) also responds to therapy

with beta-blockers,[2,4,29] reducing the number and duration of episodes of ST segment depression detectable in 24-hour Holter monitoring.

Although some agents have been effective in monotherapy[2,4] for angina at rest (angina at slow heart rates, with probable vasospasm component), it seems advisable to use calcium antagonists or nitrates, both of which have confirmed success in the control of coronary spasm.

High blood pressure (HBP)

It is agreed that beta-blockers are effective in the treatment of HBP, achieving effectiveness through its negative inotropic and chronotropic effects, with both contributing to a decrease in cardiac output which, in the short and long terms, leads to a decrease in blood pressure. These factors make beta-blockers particularly important in cases of HBP where cardiac output is high, or where there is an increased sympathetic tone.[2]

Beta-blockers are also attributed with the capacity to decrease plasma renin, the secretion of which is partly mediated by the sympathetic system. However, the role of renin reduction in HBP is not clearly established, and it was found that patients with elevated renin may even show an increase in blood pressure when treated with beta-blockers.[2] There is also no evidence that beta-blockers penetrate the blood brain barrier, thus, with a possible central effect, they are more effective when used as antihypertensives. In fact, no central effect is described, and they are effective drugs with and without lipophilic activity.[2,30] In relation to peripheral resistance, beta-blockers without alpha effect may even be responsible for its increase, as they remove opposition to the alpha stimulatory mechanisms (responsible for vasoconstriction). The vasodilator effects in the peripheral muscles are mediated by beta-2-blockers. Therefore there are advantages, theoretically, to using agents with partial agonistic capability and beta-blocking activity. Beta-blockers without vasodilator activity appear to be more effective in Caucasian and younger patients than in Black or elderly patients.[31] Since high doses are usually used in patients with HBP, beta-1 selectivity has little therapeutic value in treating hypertension.

Beta-blockers may determine a reduction in renal plasma flow, [4,28] through an overall reduction in cardiac output and/or vasoconstriction. However, in most cases, this reduction is not significant.[32] The beta-blocker tertatolol, investigated in a French study, did indeed have a beneficial effect on the renal function of hypertensive patients.[33] In the TIMS[34] (Tertatolol International Multicentre Study), in the subgroup of hypertensive patients receiving monotherapy with tertatolol, a decline was observed in serum creatinine levels in patients with pathological values on the date of inclusion. Another trial[35] with a higher number of patients confirmed this benefit in renal function in cases in which renal haemodynamics is already altered. This normalization capacity of the renal profile appears to be attributable to a renal vasodilator mechanism, independent of the interaction with alpha or beta adrenergic receptors, which was demonstrated experimentally.[36] A renal protective effect was also assigned to another drug in this class, nadolol.[7,33] Another capability of beta-blockers is the fact that they act on the presynaptic receptors, causing a smaller release of catecholamines, thereby making the beta postsynaptic blockade more effective and reducing alpha stimulation – a limiting effect of vasoconstriction (decreased peripheral resistance).[2]

Left ventricular hypertrophy induced by HBP is an independent risk factor for cardiac mortality and morbidity. Beta-blockers were shown to be effective drugs in regression of left ventricular hypertrophy detected by echocardiography, [2] although less effective than angiotensin converting enzyme inhibitors in retrospective studies.[4]

Cardiac dysrhythmias

The main action of beta-blockers is to decrease spontaneous rhythm of the sinus node or ectopic pacemakers (decrease in automatism),[2,4] constituting class II of the Vaughan-Williams classification (*Table II*). Dysrhythmias that depend on an increase in automatism, as in a context of myocardial infarction, digitalis toxicity, hyperthyroidism, and phaeochromocytoma, respond well to beta-blockers. The membrane stabilizing action is independent of the adrenergic blockade. This effect does not appear to have any significant clinical utility, as it requires higher concentrations than those used clinically.[2]

In general, beta-blockers have been clinically used whenever control of heart rate is needed, particularly in common supraventricular arrhythmias (*Table III*). In the case of Wolff-Parkinson-White syndrome, the capacity to decrease anterograde AV nodal conduction, blocking the reentrant circuit, has justified their use.[37] It has also been demonstrated consistently the

TABLE II

Electrophysiological effects of beta-blockers

Mechanisms of action	Limiting spontaneous depolarization; delaying repolarization*; membrane stabilizing action**
Effects on the action potential	Phase 4 elevation rhythm depression; extending the duration of the action potential*; Phase 0 elevation rhythm depression
Main site of action	Sinus and AV nodes
Effect on the AV node and His-Purkinje system	A-H conduction time; AV node refractory period; His-Purkinje system refractory period*
*Exclusive sotalol capacity (class III antiarrhythmic)	
**Characteristics of class I, for some drugs at high doses. It is questionable whether it confers any therapeutic benefit.	

efficacy in the prevention of arrhythmic death in patients with a history of acute myocardial infarction. The question now is whether the protective effect is a class effect, since all the tested agents are lipophilic, suggesting that the antifibrillatory effect of these drugs may be due to an effect on the central nervous system, possibly through an increase in vagal activity.[38] It was also found that beta-blockers can prevent the pro-arrhythmic effects associated with class I agents.[38]

Sotalol, the only agent of Vaughan-Williams class III to have antiarrhythmic effects, prolongs the action potential, thereby delaying repolarization. DL-sotalol has been shown to be more effective than the class I agents in preventing ventricular tachyarrhythmias.[39] Its superiority was so great that the use of class I agents as first-line treatment for ventricular dysrhythmias was no longer justified.[38] In our context, the capacity of antiarrhythmic DL-sotalol has been demonstrated which, when used as second intention treatment, proved to be effective in malignant supraventricular and ventricular dysrhythmias, with few side effects.[40] D-sotalol, which is almost devoid of beta-blocking action, did not prove to be equally effective, probably due to the proarrhythmic effect (torsades de pointes).[38] In conclusion, in addition to the known classic indications, beta-blockers are particularly recommended in patients with ischemia-induced dysrhythmias. Sotalol, due to its particular characteristics, should be used with benefit as a class III agent, especially as it has less side effects than other agents in this class (however, QT monitoring is required).

TABLE III

Beta-blockers on arrhythmia

Supraventricular	
Sinus tachycardia	Reducing heart rate, if this is clinically relevant (angina)
Auricular fibrillation	Controlling heart rate; may be useful in combination with digoxin
Auricular flutter	Controlling heart rate; may restore sinus rhythm
Paroxysmal Auricular Tachycardia	Controlling heart rate; restoring sinus rhythm; useful in prophylaxis
Ventricular	
Ventricular extra-systoles	For ischemic conditions; digitalis toxicity, mitral valve prolapsed, hypertrophic cardiomyopathy
Ventricular tachycardia	For ischemic conditions (exercise) and digitalis toxicity
Ventricular fibrillation	Proven efficacy in reducing the incidence of episodes of ventricular fibrillation and sudden death after myocardial infarction
W.P.W Syndrome	Very useful; A-V conduction time

Hypertrophic cardiomyopathy

Beta-blockers are useful in hypertrophic cardiomyopathy, [2,4,41-43] due to their negative inotropic and chronotropic effects, lowering the left ventricular outflow tract gradient at rest and during exercise, and improving ventricular diastolic function. Beta-blockade has proven to be effective in relieving symptoms of dyspnea, fatigue and syncope, which are common in this clinical situation.[41-43] Nevertheless, there is no evidence that therapy with beta-blockers improves the prognosis or reduces the incidence of sudden death in this clinical entity.[2,41,43]

The most commonly used agent has been propranolol, which is sometimes administered at high doses.[4,41] Associations with calcium antagonists, verapamil or diltiazem (used as an alternative, due to its negative inotropic action) should be avoided, as these promote the adverse effects of beta-blockers.[41,43] Sotalol, although yet to be proven, may be important in the treatment of hypertrophic cardiomyopathy.[43]

Dilated cardiomyopathy

Initially it was thought that beta agonist stimulation of a failing heart would be useful in treating congestive heart failure. However, recent evidence on chronic adrenergic stimulation revealed: 1 - high adrenergic plasma levels in patients with heart failure, 2 - cardiac catecholamine depletion, 3 - direct toxic effect on the myocardium, 4 - complex changes in the beta-receptor/ adenylate cyclase (making the beta--receptors less sensitive); 5 - decrease in the number of beta-receptors.[2,44,45] Thus, theoretically, beta-blockers exert a beneficial effect, since they do not cause functional changes in the receptors, but give protection against intense adrenergic stimulation, protecting the cardiomyopathy process.[2,44,45]

Metoprolol has been one of the most studied agents in the context of dilated cardiomyopathy. In one trial, [44] metoprolol, initiated at very low doses (initial dose of 6.25mg twice daily and increased to an average dose of 103 mg/day if tolerated), was associated with an increased density of beta adrenergic receptors, improved cardiac output at rest, and improved response to catecholamine stimulation. Waagstein and colleagues[45] investigated metroprolol at similar doses, but in patients with more severe conditions (classes III and IV of the New York Heart Association classification), using a protocol of therapy withdrawal, with subsequent resumption. Beneficial hemodynamic and clinical effects were achieved, withdrawal of the therapy was harmful in the vast majority of patients, and resuming the therapy was beneficial. In these two trials, there was an increase in density of the cardiac beta receptors.[44,45]

In a recent CIBIS[46] (Cardiac Insufficiency Bisoprolol Study), bisoprolol was tested against placebo in 641 patients. Of these, 320 highly symptomatic patients (95% in class III and 5% in class IV) were randomized to bisoprolol, with the participation of our country and involving a two-year medical follow-up. It was concluded that there was a functional benefit in the group taking bisoprolol, but no benefit was found for the mortality in relation to its use. Analysis of the subgroups enabled us to determine that paradoxically, there was a greater benefit in non-ischemic cardiomyopathy, for reasons which are unclear. Interestingly, the complications that led to withdrawal from the trial protocol (especially worsening of the heart failure) did not differ significantly between the groups treated or not treated with bisoprolol.

Clearly, further studies are needed to prove a clear benefit in mortality in patients with dilated cardiomyopathy taking beta-blockers. We believe that the routine use of these drugs is premature, since the side effects, in this pathology, are significant.

Mitral valve prolapse

Beta-blockers are useful for relieving symptoms of precordialgia and palpitations associated with this entity, as well as reducing the frequency of supraventricular arrhythmias.[2,4]

Dissecting aneurysm of the aorta

Beta-blockers play an important role in the initial treatment of this emerging condition, preventing the reflex tachycardia caused by other hypotensive agents, and decreasing inotropism. Agents such as propranolol and metoprolol were used intravenously.[2,47] Another drug, labetalol, seems to be quite useful in maintaining low blood pressure levels, due to its combined alpha and beta antagonism .[48]
The prophylactic use of beta-blockers is recommended for high-risk patients (e.g. Marfan syndrome).[2,47]

Congenital long QT-interval

Hereditary long QT-interval is associated with well--defined syndromes (Jervell-Lange-Nielsen, Romano--Ward), and sometimes occurs sporadically.[49] It has been attributed to dysautonomia of the sympathetic system, associated with syncope and sudden death. Propranolol has been the most frequently reported drug in the literature for the management of this clinical entity, reducing episodes of syncope and improving the prognosis.[2,4,50]

Tetralogy of Fallot

Used as palliatives for their limiting action of adrenergic stimulation on the right ventricular infundibulum, the drugs are useful in the treatment of hypoxemic crises and hypercyanotic attack. Their use decreases the incidence of hypoxemic crises.[2]

Incidental effects of beta-blockers (Table IV)

Heart failure

Some clinical conditions depend on sympathetic stimulation to preserve heart function. Thus, the negative inotropic effects of beta-blockers cause failure of the left ventricle. Although some authors[4,51] advocate

TABLE IV

Incidental effects of beta-blockers

Sinus bradycardia
Atrioventricular blockade
Congestive heart failure
Bronchospasm
Raynaud's phenomenon
Intermittent claudication
Hypoglycemia
Hyperlipidaemia
Depression
Sleep disorders
Male sexual dysfunction
Gastrointestinal disorders (diarrhea, nausea, epigastralgy)
Purpura and agranulocytosis (rare)
Rebound effect after abrupt withdrawal

the preferential use of agents with associated ISA or antagonism, it has not been conclusively proven that drugs with these characteristics are more effective in preserving left ventricular function.[2]

Sinus node dysfunction and atrioventricular conduction disturbances

If there is a defect, partially or completely, in AV conduction, the use of a beta-blocker can cause a severe bradyarrhythmia, which is milder for drugs with ISA.[2,4] In elderly patients, beta-blockers should be introduced at low doses, in order to prevent these disturbances.

Beta-blocker withdrawal syndrome

Chronic use of beta-blockers can cause an increase of beta adrenergic receptors and endogenous catecholamines. Thus, abrupt withdrawal leads to an excessive adrenergic stimulation, leading to a sudden increase in oxygen consumption and disrupting the delicate balance in ischemic heart disease, with possible exacerbation of angina, or even causing acute myocardial infarction. To avoid this phenomenon, the beta-blocker dose should be gradually reduced whenever its withdrawal is required (e.g., before exercise testing, reduce the dose for 5 days, then do not give beta-blockers within two days of the test).[52] For tertatolol, a drug without ISA, De Blasi and colleagues[53] suggest its capacity to prevent this effect of therapeutic suppression, since it would cause a reduction in the number of receptors rather than an increase, as described for other beta-blockers.

Overdose

Suicide attempts, in particular, are treated with inotropic support infusion (dobutamine).[2] The patient should then be monitored for signs of the withdrawal effects mentioned above.

Bronchospasm

None of the beta-blockers should be considered safe in cases of bronchospastic disease.[2,4,7] If absolutely necessary, a beta-1 selective agent should be used. Beta-blockers with ISA or alpha-blocking capability, which are probably less aggressive, will nevertheless provide less protection.

Bisoprolol, a very selective agent that has been recently been investigated, is one of the most useful agents for patients with bronchospasm.[7]

Peripheral vascular disease

Beta-blockers act at the peripheral level by decreasing cardiac output and skeletal vasodilatation blockade mediated by the beta-2 receptors, resulting in vasoconstriction by non-blocked alpha activation. Thus, the presence of ISA, antagonism or beta-1 selectivity is preferable in patients with peripheral vascular impairment.[4] The most common incidental effects of beta-blockers include Raynaud's phenomenon and intermittent claudication.

One trial[54] suggests that beta-blockers can be safely used in patients with mild to moderate peripheral vascular disease (regardless of selectivity), but they are absolutely contraindicated in the presence of pre-existing Raynaud's phenomenon. In patients with severe peripheral vascular disease, small changes in perfusion pressure or vascular tone may be very serious (gangrene), therefore beta-blockers should be avoided. Finally, all patients should be closely monitored for changes in their symptoms during the introduction of beta-blockers.[2,54]

Diabetes mellitus

The presence of diabetes mellitus is not a contraindication to the use of this drug class, even if the patient is insulin dependent. The beta blockade, in fact, prevents the physiological response to hypoglycemia

(muscle glycogenolysis is mediated by beta-2 receptors, with selective agents being preferred). It was also shown that in healthy individuals, beta-blockers do not cause any change to fasting blood glucose.[2,7] A marked decrease in the manifestations of hypoglycemia-induced catecholamine depletion (tachycardia, anxiety, tremor) should be taken into account. A warning sign, unchanged by beta blockade, is diaphoresis.[2]

Lipid metabolism

Nonselective beta-blockers increase the levels of VLDL by blocking adrenergic stimulation of lipoprotein lipase enzyme. It was also shown that beta-1 and beta-2 agonists increase the lipase activity, while alpha agonists inhibit it.[55] Thus, in general, therapy with agents without ISA does not cause significant changes in LDL cholesterol, but raises triglycerides and lowers HDL[4]. The commonly studied drug is propranolol, which can increase the concentration of triglycerides by 50% and reduce HDL cholesterol by 15%.[56]

In terms of risk/benefit ratio for coronary atherosclerosis, it should be borne in mind that beta blockade decreases plasma HDL cholesterol concentration (associated with a lower risk of coronary heart disease).[57] The balance, however, is positive, and overall, the benefits of beta-blockers outweigh their disadvantages.[55]

Actions on the central and vegetative nervous system

Given that liposoluble agents are able to surpass the blood brain barrier, side effects have been associated with them, such as sleep disturbances, hallucinations and depression. However, more extensive evidence is needed, to show that liposoluble agents have beneficial effects in this particular action.[2,56] For example, atenolol and metoprolol cause a similar number of central side effects, despite the difference in lipid solubility.[56] In fact, the central action of liposoluble agents appears to involve mainly sleep disorders (insomnia, nightmares, anxiety). Other measures of mood, sexual function or psychomotor function are not closely correlated with lipid solubility.[56]

Another important effect to consider is sexual impotence in males, which can be caused by beta-blockers. Other effects are decreased libido and delayed ejaculation, particularly in hypertensive male patients, described for both selective and non-selective drugs.[23]

Other drug interactions

The most important interactions for clinical practice include: 1-aluminum hydroxide: decreases the absorption and therapeutic effect, 2 – indomethacin: inhibits the antihypertensive effect of beta-blockers, 3 - oral anti-diabetics: potentiation of hypoglycemia; 4 – calcium antagonists: effect on conduction and inotropism, potentiation of bradycardia and myocardial depression (use with caution); 5 - tricyclic antidepressants: inhibit the negative chronotropic and inotropic effects of these drugs; 6 – cimetidine: decreases the liver metabolism of beta-blockers, with subsequent potentiation of effects.[2,56]

How to choose a beta-blocker

In relation to the adverse effects, it is difficult to compare the various trials conducted because they have different designs and methodologies, and their patients are in different clinical stages. A comparative review of the side effects did not prove, in general, any difference in the level of adverse effects between selective and non-selective beta-blockers.[58] The best choice of beta-blocker depends on the particular pharmacokinetics of the drug, in conjunction with the patient's medical conditions. ■

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