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Beta blockers and their appropriate use in patients with dyslipidemia

Los betabloqueadores y su adecuado uso en pacientes con dislipidemia

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To the Editor:

Oates and Brown[1], leading scholars and researchers in the field of pharmacology of antihypertensive drugs, pose in their basic text that nonselective beta blockers, without intrinsic mimetic activity, increase plasma triglyceride levels, and decrease high-density lipoproteins (HDL) without changes in total cholesterol; while beta blockers with intrinsic sympathomimetic activity (ISA) have little or no effect on blood lipids, or increase HDL, which plays protective functions[1,2]. However, It have been found that in the community there are a number of hypertensive patients with associated dyslipidemia, diabetes mellitus and ischemic heart disease, who are treated with beta blockers such as propranolol (nonselective beta blocker) and atenolol. This group differs greatly in their pharmacokinetic and pharmacodynamic characteristics; therefore, there is a major controversy as to its proper use.

The pharmacodynamic characteristics of beta blockers allow the distinction between various types of drugs, with different influences on the cardiovascular profile. Non-cardioselective beta blockers increase plasma levels of triglycerides and lower HDL. The effects on lipids of the selective beta blockers that also have ISA are almost zero; even those with alpha activity have favorable effects on the lipid profile[1-4].

This group of drugs, when used without considering the lipid profile of each subject, can subtly affect patients who suffer from a disorder in this area. We are aware that now, in the primary health care, these studies cannot be performed because of their high costs[5]. However, it is necessary to bear in mind the classification of beta-adrenergic blocking agents to make the best use of them in these patients, because, from our point of view, there is an indiscriminate use of these drugs, not only in hypertensive patients with lipid disorders, but also in those with diabetes mellitus and ischemic heart disease.

It is essential to establish a comprehensive therapeutic approach for patients with multiple risk factors. It is very important to consider both, the interventions that will act synergistically in reducing cardiovascular risk, and those that – although may be useful in the treatment of one of the risk factors – can be harmful to others and even to the general development of cardiovascular disease. The goal should always be choosing the optimal treatment for our patients[6].

Patients should be treated individually, as lipid disorders are risk factors to keep in mind when indicating a beta-blocker or a diuretic drug, because these groups of drugs adversely affect lipid profile[1,2,5].

According to the blocking β-adrenergic receptors, these drugs can be classified into:

- Cardioselective beta blockers (relative selectivity

over β1 receptors): acebutolol, atenolol, betaxolol, bisoprolol, metoprolol, nebivolol.

- Nonspecific or nonselective beta blockers: propranolol, nadolol, timolol, Alprenolol, bopindolol, carteolol, penbutolol.
- Those with α- and β-adrenergic blocking activity: labetalol, carvedilol, celiprolol.

Besides the selectivity over β receptors, it is also important to consider the ISA, that is, that they are able to stimulate the receptor first and then block it. The following drugs have ISA: acebutolol, alprenolol, bopindolol, carteolol, penbutolol and pindolol[1-4].

According Mancia *et al.*[7], these drugs are not considered of choice in the initial treatment of hypertension (HT), when there are alterations in the lipid profile, as they cause increased plasma triglycerides by inhibiting the activation of lipase, adipocyte hormone sensitive; and by decreasing lipolysis and fatty acid release, they decrease HDLC and increase the LDLC (low density lipoprotein cholesterol), these effects are associated with the blockade of β2 receptors[1,2,8].

Most chronic treatment with these drugs produce increased triglycerides and decreased HDLC; the effect is less with cardioselective beta blockers, but it may also appear. Carvedilol and celiprolol are those with less effect on the lipids[1-3].

Some cardioselective beta blockers, such as nebivolol and carvedilol, may be well tolerated without affecting glycemic control and may improve some components of metabolic syndrome, as they normalize the lipid profile in dislipidemic subjects[1,2,4].

Some authors prefer α1 antagonists like prasozin, doxazosin and terazosin. Doxazosin lowers triglyceride levels, total cholesterol, LDL and very low density lipoproteins (VLDL). Furthermore it raises HDL levels and the total cholesterol/HDL ratio. These effects appear to be maintained also with the combination of diuretics and beta blockers[1,2,9].

However, it is important to remember once more the comprehensive and individualized treatment of patients with cardiovascular disease. While it is true that in the possibility of two equally effective antihypertensive therapies, the one that produces beneficial variations in the lipid profile would be the chosen one, do not forget that this is not the only option. An alternative is to choose the most effective drug in controlling hypertension (even if it creates a less preferred lipid profile) and use, if necessary, other therapeutic measures that improve dyslipidemia[10]. For example, a patient with difficulties to control hypertension may require the use of a thiazide. A beta blocker or a loop diuretic may be chosen in a patient with a history of heart failure. Maybe the side effects of other antihypertensive medications have restricted our choice to drugs that are damaging for dyslipidemia. In these cases it is advisable to monitor the impact on cholesterol and triglyceride levels, and, if necessary, these alterations must be treated with other hygiene-dietary measures[11].

According to Lavie *et al.*[12], the British Society of Hypertension, in their treatment algorithm, has removed beta blockers for the first line of drugs for hypertension, as outlined in recent recommendations of the National Institute for Health and Clinical Excellence. It is stated: "Beta blockers are not preferred drugs in the initial treatment of hypertension, but they are an alternative to blockers of the renin-angiotensin-aldosterone system in patients younger than 55 years, if these drugs are not well tolerated"[12].

The angiotensin converting enzyme (ACE) inhibitors may be a therapeutic option in the treatment of hypertensive patients with lipid disorders. This group of drugs has a slight beneficial effect, apparently mediated by a decrease in insulin resistance, the raising of HDL and a lowering of triglyceride levels. This action has been found mainly in patients in whom ACE inhibitors are associated with diuretics, although such changes have not been demonstrated in all studies. A class effect in IECA lipid modification has not been demonstrated either[1,2,4,5,13]. It could also be said that they are suitable for use in the treatment of hypertension when there is associated dyslipidemia. Moreover, in the case of the angiotensin II receptor antagonists, due to their recent appearance in clinical practice, there is not much information, but its effect seems to be neutral with regard to the lipid profile[14].

It is very important to note that hypertensive patients are not treated with a single drug group; in many cases they also take a diuretic that can also affect the lipid profile[1,2]. The negative influence of diuretics in this regard has been known for years; however, most studies found this association with

higher doses than those currently recommended in most patients for the treatment of hypertension. Thiazide diuretics elevate LDL and triglyceride levels and the same seems to happen with loop diuretics. It is possible that torasemide and indapamide have less effect on the lipid profiles[1,2,5].

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Heart rate turbulence: a useful parameter in predicting sudden cardiac death

Turbulencia de la frecuencia cardíaca: un parámetro útil en la predicción de muerte súbita cardíaca

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To the Editor:

Prevention of sudden cardiac death (SCD) is one of the most important challenges in modern cardiology. Some variables that increase the risk of SCD have been identified through the years, with more or less validity in clinical practice. In 1999, Schmidt *et al*.[1] published a paper in which they developed a new concept called heart rate turbulence (HRT). This concept describes the physiological heart rate fluctuations that are secondary to ventricular extrasystole (VE). These changes are the initial acceleration of heart rate followed by a deceleration. Although these changes had been identified previously [2], these researchers were able to quantify them for the first time. It is stated that HRT is a measure of the body's autonomic response after disturbances in blood pressure, as a result of the VE. Changes in this parameter have a relevant clinical significance, given its effectiveness in predicting SCD after an acute myocardial infarction (AMI) and other heart diseases.

The main theory explaining the HRT states that this is a form of ventriculophasic sinus arrhythmia, which occurs as a result of nerve reflexes secondary to VE. The initial acceleration results from a transient vagal inactivation and a sympathetic activation in response to an inefficient ventricular contraction. After this process, deceleration occurs, due to the restoration of blood pressure levels as a result of the increase in ventricular filling[1-4].

HRT measurement

Turbulence measurement is performed by the Holter monitor. The two most frequently used measurements for the HRT are turbulence onset (TO) and turbulence slope (TS). The former relates to the acceleration of sinus rhythm after the VE, while the latter allows the measurement of deceleration following the initial acceleration. In healthy subjects, the acceleration of rate after the premature beat is characterized by negative value of TO. The reference value is 0%. Values of this variable < 0% indicate acceleration, while values > 0% indicate deceleration. The presence of positive values indicates abnormality. In the case of the TS, a value of 2.5 ms/RR has been set. A value below this figure is considered abnormal[5].

$$TO = [(RR_1 + RR_2) - (RR\_2 + RR\_1)]*100/(RR\_2 + RR\_1)$$