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The history of beta blockers

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Abstract

The history of beta blockers dates back to 1960 with the discovery of propranolol by Scottish James W. Black, who also received the Nobel Prize in 1988. Being the first representative of the beta blocker class, propranolol has long been used in cardiology, in the treatment of portal hypertension in patients with cirrhosis (still used today) as well as in the treatment of hyperthyroidism and glaucoma. Later, cardioselectivebeta blockers, antiglaucoma (timolol), alpha beta blockers (carvedilol, labetalol), water-soluble (atenolol, nadolol, sotalol) and liposoluble (metoprolol), intrinsic sympathomimetics (acebutolol, pindolol) and metabolically neutral (bisoprolol, nebivolol) developed. Beta blockers are commonly prescribed in patients with cardiovascular disease such as: high blood pressure, congestive heart failure, myocardial infarction, angina pectoris, ischemic heart disease. Although they are part of the second class of antiarrhythmic drugs, they are rarely prescribed in the treatment of arrhythmias (they are used to treat tachycardia, whether due to anxiety, hyperthyroidism or lithium therapy). Of particular importance is the use of beta blockers in patients suffering from heart failure, which are important in decreasing mortality and morbidity according to guidelines. In heart failure, beta blockers have long been contraindicated until 1975 when a clinical trial of 7 patients demonstrated the benefits of adrenergic blockade on cardiac function. Pharmacological treatment in patients with cirrhosis is performed with non-selective beta-blockers (BBNS)

(propranolol, nadolol). BBNS reduces the risk of bleeding from 24% to 15% after 2 years.

Key words beta-blockers, cardiology, hypertension, cirrhosis, treatment.

Introduction

In the early 1960s, James Black created propranolol, the first beta-blocker for clinical use, orally administered. Black wanted to create a heart rate-lowering drug, a desirable effect on angina, but another effect of beta-blockers surprised researchers was blood pressure lowering. They also have a positive effect on heart rhythm disturbances and decrease the risk of mortality if administered after myocardial infarction.

Indeed, the beta-adrenergic blockers have provided us with a great clinical legacy for now and in years to come (Frishman, 2008a).

The history of beta-blockers begins about 45 years ago. Initially they were applied for their anti-ischemic and antihypertensive effects, but contraindicated in heart failure. In the 1980s and 1990s, their use in heart failure was radically reconsidered, with beta-blockers becoming one of the major drug classes that improved prognosis in this pathology, provided they were prudent and progressively increasing.

During this time, beta-blockers have proven useful in other pathological situations - arrhythmias, obstructive hypertrophic cardiomyopathy, aortic dissection, and non-cardiac surgery.Recently, their use in hypertension has become increasingly controversialpressure.

Beta-blocker studies began in 1958 in England, and it was based on the idea that such compounds could be obtained by some structural changes of isoprenaline, adrenomimetically acting mainly on β receptors. Based on this idea, dichloroisoprenaline has the ability to inhibit the effects of isoprenaline in the heart and vessels, but also maintains β-adrenomimetic properties.The adrenergic beta-blocker class was born in 1960, with the discovery of propranolol by the Scottish James W. Black (who received the Nobel 1988 Award). Propranolol, derived from alpha-naphthol, was introduced into therapy in 1965 in England.

Being the first representative of the class, propranolol has been used for a long time both in cardiology and in the treatment of

hyperthyroidism, essential tremor, headache, cirrhosis, tensional headache, portal hypertension and glaucoma.

The calming effect of propranolol and other beta-blockers has been used swiftly for other purposes as well. The musicians have begun to use it since the 1970s to reduce the effects of nervousness during concerts. For sportsmen, beta-blockers are listed on the list of prohibited substances.

In recent years beta-blockers have begun to be increasingly used by students during the exams. The most commonly used are propranolol, followed by metoprolol and atenolol. Over the years, it has been discovered that these active substances can be used to treat a large number of diseases both individually and in combination with other active substances. Subsequent studies have led to the discovery of beta-blockers belonging to generation I-a, phenylethanolamine derivatives.Of these, labetalol is a beta-blocker with a particular profile, blocking α-adrenergic receptors. It can be used in patients with angina pectoris and hypertension. The second generation of beta-blockers is represented by aryloxy-propanolamine derivatives. They were synthesized for the favorable effect, both for the increase in antagonistic activity and for the decrease in agonist effects. Carvedilol, like labetalol, is a beta blocker that also possesses blocking activity on alpha 1 receptors. Carvedilol possesses antioxidant and antiproliferative action on smooth muscle cells vascular. At the same time, it presents protective effect at the cardiovascular and neuronal level and has proved to be beneficial in heart failure.

In 1981, Lebrecet al.performed the first randomized clinical trial involving 74 cirrhotic patients with a history of variceal bleeding. This study documented a significant reduction in rebleeding in patients on propranolol as compared to placebo (Lebrec, 1980). Since then, there has been a growing interest among hepatologists regarding the role of non-selective β-blockers (NSBB) in decreasing portal hypertension and preventing its complications (Lebrec,Nouel,Corbic&Benhamou, 1980).

In addition to propranolol and nadolol, carvedilol has been investigated as a promising NSBB with the additional property of vasodilatation due to its intrinsic anti-α1 adren- ergic activity and its capacity to enhance the release of nitric oxide (Bosch, 2010). Thus, carvedilol reduces portal pressure not only by decreasing portal-collateral blood flow (as all other NSBB) but also by diminishing the functional component of hepatic vascular resistance which is increased in cirrhosis. Due to these effects, this drug may cause a higher risk of arterial hypotension leading to discontinuation of treatment. Indeed, a

reduction in mean arterial pressure has been documented in patients on carvedilol, proportionally to the dosage(Bañares, Moitinho, Piqueras, Casado, García-Pagán, de Diego & Bosch, 1999).

Beta-blockers selectively bind beta-adrenergic receptors (β), producing a competitive and reversible antagonism of beta-adrenergic stimulation. The most studied beta-adrenergic receptors ar type 1 and type 2. Consequently, β-blockers counteract the action that the adrenergic system mediates through these receptors, action ranging from one type of tissue to another, but also from one physiological state to another.

The most well-known classification of β-blockers is based on the selectivity with which they antagonize the two types of β-receptors: non-selective, which block both β1 and β2 receptors (propranolol, sotalol) and selective β1, which predominantly block β1 receptors (bisoprolol, metoprolol, atenolol). Selectivity is dose dependent.

Non-selective beta-blockers exert a number of undesirable effects by blocking β2-receptors, such as: reducing vasodilatation and β2-dependent bronchodilation, or altering the metabolic balance of glucose and lipid. The reduction of these effects was achieved by increasing β1-selectivity and by creating molecules with associated effects such as nebivolol- with peripheral vasodilator action by β2 or β3 -receptor mediated nitric oxide (NO), carvedilol and labetalol - by β1-blockade or celiprolol - by β2-adrenergic agonism. Another classification divides β-blockers into lipophilic and hydrophilic. Lipophilic drugs (propranolol, metoprolol) have short half-life (1-5 h), hepaticallymetabolised and cross the blood-brain barrier with greater probability of central nervous system side effects. Hydrophilic (atenolol, esmolol) have longer half-life (6-24 h) and is eliminated mainly in the kidney.

The β-blockers are very important class of drugs because their high use in cardiovasculare disease. The history of β-blockers dates 100 years ago. Since then, the investigators stated the idea that the mechanism of action of catecholamines is that of binding selectively to receptor-like structures and this is the way of their pharmacological actions (Frishman, 2008b).

Conclusion

The use of beta-blockers in general pathology increased so much, that there is almost no therapy domain with any interference of these substances.

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