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Review

Propranolol: A migraine prophylactic since the 1960s

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Abstract

Introduction
Propranolol was the first non-selective beta-adrenergic blocker to be developed. Initially it was used in the treatment of cardiovascular diseases, but since the 60's it has been used in the prevention of migraine.

Objective
The objective of this study was to know the history of propranolol and its use as a migraine prophylactic.

Methods
This study was an integrative literature review using articles with historical data on propranolol, from its origin in cardiology to its indication in the preventive treatment of migraine.

Results
Propranolol was described in 1962 for the treatment of cardiovascular diseases. In the same decade, it was prescribed for the preventive treatment of migraine and, recently, included in the consensus of the Brazilian Headache Society.

Conclusion
Although propranolol was initially synthesized for the treatment of heart disease, it has proved to be an effective drug in preventing migraine attacks.

Keywords:
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The origin of propranolol

Propranolol was the first non-selective beta-adrenergic blocker to be developed. It was synthesized from the insertion of an oxymethylene group in the structure of pronethalol, in 1962, by the Scottish pharmacologist James Whyte Black (1924-2010) and commercialized in 1964.[1–5]

It is particularly indicated in the treatment of cardiovascular diseases such as systemic arterial hypertension, angina pectoris, hypertrophic obstructive cardiomyopathy, cardiac arrhythmias, hypertrophic subaortic stenosis and mitral valve prolapse and prevention of myocardial infarction.[6–8] However it is also used in the treatment of essential tremor and in the prophylaxis of migraine.[9]

In the treatment of cardiovascular diseases, its mechanism of action is known. It blocks beta-adrenergic receptors, inhibiting sympathetic stimulation. This results in reduced resting heart rate, cardiac output, systolic and diastolic blood pressure, and reflex orthostatic hypotension.[10]

Propranolol should not be used in patients with cardiac decompensation, sinus dysfunction syndrome or second and third degree heart block, severe bradycardia, history of bronchospasm or bronchial asthma, chronic obstructive pulmonary disease, metabolic acidosis, diabetes and Prinzmetal's angina.

Who was Sir James Whyte Black

James Whyte Black was a Scottish pharmacologist who was born on 14 June 1924 and died on 23 March 2010, aged 85. He was professor of physiology at the University of Glasgow in Scotland; and Analytical Pharmacology at the Rayne Institute at King's College London Medical School, London.[11]

Black was responsible for discovering two drugs: the first beta-blocker (propranolol), in 1962; and the first selective histamine H2 antagonist for the treatment of stomach ulcers (cimetidine), in 1975.[11]

His research and discoveries developed his deep fascination with receptor theory as the foundation of pharmacology and drug discovery. He won the Nobel Prize in Medicine in 1988 for his method of drug invention, which consisted of building molecules around the structure of a natural chemical activator of a pathway involved in the etiology of a disease.[3]

The first prescriptions for migraine

Propranolol was first prescribed as a migraine prophylactic in the USA in 1968 by John Graham. Shortly afterwards, he stopped using it because that drug had not been approved by the Food and Drug Administration (FDA) to prevent migraine attacks.[12] A few years later, Graham performed a double-blind, placebo-controlled study and sugered that propranolol to be effective in preventing migraine.[13]

Still in 1968, Edgard Raffaelli Júnior, a disciple of John Graham, was the first physician in Latin America to prescribe propranolol as a preventive drug for migraine. He used propranolol on himself from 1968 until 1976, when he had the last headache attack, of short duration and mild intensity.[12,14] Like Raffaelli, most headache pioneers tested drugs on themselves due to the lack of available options, as seen in the first publications in 1968.[15]

At that time, in Brazil, this drug had not been approved by the National Health Surveillance Agency for patients with migraine. As a result, Raffaelli faced problems with the prescription of propranolol because there was no reference to its indication for headache in the package insert. Some patients refused to use it because they did not have high blood pressure or heart disease.[12,14]

In the early 1970s, studies began to appear demonstrating the effectiveness of propranolol in preventing migraines[16–20], but as it was not included in the package leaflet, Raffaelli decided to formulate all of his prescriptions. At that time, compounding pharmacies in São Paulo (Brazil) only prepared magistral formulas (those that appeared in medical books). Raffaelli was the first Brazilian doctor to create non-magisterial formulas.[12]

Propranolol and migraine

Prophylactic treatment of migraine came from Sicuteri's studies when he attributed to serotonin a prominent role in its genesis.[21] Drugs that interfered with serotonin metabolism were tested. Initially, methysergide and pizotifen; then propranolol and amitriptyline.

Although propranolol has been used for migraine prophylaxis for over 50 years[12], only in 2002, Brazilian Headache Society appointed an ad hoc Committee with the purpose of establishing a consensus on the prophylactic treatment of migraine and of preparing recommendations to be disseminated among physicians. This Consensus recommended the use of tricyclic antidepressants, calcium channel blockers, serotonin antagonists, antiepileptic drugs

and beta-adrenergic blockers, including propranolol.[22]

Propranolol has been widely used in migraine prophylaxis as a first-line medication.[23,24] Despite the existence of consensus and guidelines that guide its prescription, many Brazilian doctors do not know how to prescribe this medication. They usually prescribe propranolol, wrongly, once a day or in inappropriate doses or even in long-term preparations that are not effective. The recommended dosage of propranolol ranges from 40 mg to 240 mg, two or three times a day, orally. It should start with low doses that can be gradually increased, according to the patient's response.[25-27]

Its exact mechanism of action in migraine prevention is not fully understood, but it lacks intrinsic sympathomimetic activity. Propranolol is believed to inhibit nitric oxide production by blocking kainite-induced currents and to have a synergistic effect on N-methyl-d-aspartate (NMDA) blockers, which reduce neuronal activity and have membrane-stabilizing properties.[28]

Other authors have described migraine treatments in depth, including propranolol. The proposed mechanisms that could be cited are the inhibition of noradrenaline release due to the blockade of prejunctional beta-receptors; the reduction of firing rates at the locus ceruleus, the most important adrenergic nucleu in the brain; and the reduction of the noradrenaline synthesis thru the action at the enzyme tyrosine-hydroxylase. In addition, an action downregulating 5HT-2b and c receptors is also a suggested effect.[29]

Conclusion

Although propranolol was initially synthesized for the treatment of heart disease, it has proved to be an effective drug in preventing migraine attacks.

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