

THE USE OF BETA-BLOCKERS IN GENERAL PATHOLOGY

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Abstract: *The use of beta-blockers in general pathology increased so much, that there is almost no therapy domain with any interference of these substances. This paper describes the use and the action of the beta-blockers in the following pathologies: pheochromocytoma, Tetralogy of Fallot, hypertrophic obstructive cardiomyopathy, aorta dissecting aneurysm, mitral valve prolapse, thyrotoxicosis, orthostatic hypotension, subarachnoid hemorrhage, glaucoma.*

Keywords: *beta-blockers, use, action*

Rezumat: *Utilizarea medicamentelor beta-blocante în patologia generală a luat amploare, astfel că aproape nu există domeniu al terapiei fără interferența cu aceste substanțe. În acest referat sunt redată utilizarea și acțiunea beta-blocantelor în următoarele patologii: Feocromocitomul, Tetralogia Fallot, Cardiomiopatia hipertrofică obstructivă, Anevrismul disecant de aortă, Prolapsul de valvă mitrală, Tirotoxicoza, Hipotensiunea ortostatică, Hemoragia sub-arahnoidiană, Glaucomul.*

Cuvinte cheie: *beta-blocante, utilizare, acțiune*

vasoconstriction, arrhythmias.

The administration of only one beta-blocker may react in an alfa activity that is not counteracted and in an excessive blood pressure increase. If the pre-operative preparation is properly elaborated, the intra-operative care and surgical response will be favourable. A phentolamine perfusion acts against the blood pressure, and I.V. injection with Propranolole is well received, as prophylaxis against supraventricular arrhythmias that may be threatening. As for ventricular arrhythmias, there are authors who prefer the use of lidocaine.

Pheochromocytoma associated with pregnancy is a major risk factor and generates numerous deaths. The mother should be treated with orally administrated Phenoxybenzamine in association with beta-blockers until the C-section by choice when, if possible, the tumour should also be removed.(1)

Tetralogy of Fallot

Tetralogy of Fallot is a complex cyanogenic malformation, characterized by: obstruction of the outlet right ventricle, flaw of the subaortic big ventricle septum, septum defect with overriding aorta, and right ventricle hypertrophy. This is the most common cyanogenic congenital malformation, comparable to a longer surviving, representing about 2/3 of the cardiomyopathies registered in adults and children over 5.

Patients suffering from the **Tetralogy of Fallot** show sometimes severe cyanotic attacks and syncopes. These attacks are frequently associated with the suppression of blood flow in the right ventricle and loss of systolic breath. This phenomenon seems to be due to the beta-stimulation of the right ventricle flow tract that is hypertrophied by the effect of catecholamines. This means that there is a reason for the use of beta-blockers. Intra venous administration of Propranolole corrects and improves the pulmonary arterial flow and the saturation of the arterial oxygen.

The long term treatment with oral Propranolole in adequate doses (up to 6 mg/Kg/day or more) is extremely efficient in the elimination of the syncopal attacks and, at the same time, it improves the physical effort endurance, usually presenting no side effects. Sometimes, there are stress syncopal attacks. Oral administration of Propranolole is sufficiently efficient and is preferably to the surgical-palliative junction treatment

INTRODUCTION

General aspects

After having described the use of the beta-blockers in: arterial hypertension, ischemic cardiomyopathy and myocardial infarction, hearth rhythm disorders, cardiac insufficiency – we continue with the presentation of their use in other fields of pathology.

Pheochromocytoma

Pheochromocytoma is characterized by the secretion of higher serum levels of noradrenalin and of adrenaline sometimes, with severe arterial pressure and arrhythmias, elements that offer important arguments for the use of alfa and beta-blockers, substances that oppose the peripheral effects of noradrenalin and adrenaline.

Phenoxybenzamine is an alfa-blocker, constantly used in the treatment of arterial hypertension in Pheochromocytoma and is more efficient when associated with the beta-blockers, with a view to counteract Phenoxybenzamine increased beta-activity.

The most frequently used beta-blocker is the Propranolole, and this combination sets up the basis for the preparation of the surgical removal of Pheochromocytoma, removing, at the same time, certain problems such as: hypovolemia associated with

usually practiced in order to gain time until surgery for final prosthesis. This method is also applied to other congenital patients with damaged cardiac anatomy, such as pulmonary atresia. In corrective surgery, mortality is higher within the first 18 months of life, and Propranolol may normally be administered for a period of time that allows a safe surgery when the child is older.(2)

Obstructive hypertrophic cardiomyopathy or hypertrophic subaortic stenosis

Obstructive hypertrophic cardiomyopathy or hypertrophic subaortic stenosis consists of a variable obstruction of the left ventricular flow tract, mainly brought about by hypertrophy of inter-ventricular septum. Hypertrophy is not related to effort increase but is an anomaly of the myocardial cells that is not met at the classic left ventricular hypertrophy. This type of hypertrophy is genetically transmitted as an autosomal dominant inheritance. Patients usually show an asymptomatic subaortic or mitral systolic breath (because of the associated mitral regurgitation), but most patients develop symptoms such as: effort dyspnea, chest angina, tremors, lypothimias or an almost constant physical exhaustion in the following years. The disease progresses with an annual mortality rate of 3-4%, usually a sudden death. No specific prognosis signs are shown except for a "malign" family history of premature – sudden deaths.

The pressure gradient of the flow tract may appear only due to sympathetic stimuli such as an Isoprenalin perfusion or the physical effort. The intra venous administration of the beta-blockers usually diminishes this gradient and improves compliancy or the left ventricular distensibility. Sudden death is usually related to physical effort.

Therefore, the long term use of beta-blockers is justified; beta 1 blockers bring the highest benefits. Disease symptoms may be isolated or radically modified and the number of sudden deaths may decrease, provided that patients are administered an optimum dose of beta-blockers, such as Propranolol - 320-460 mg/day. In spite of the beta-blockers treatment, the disease progresses but this should not be a motive to cut the beta-blockers treatment.(3)

Symptomatic children and pregnant women suffering from obstructive hypertrophic cardiomyopathy benefit from beta-blockers treatment. Physicians do not always agree on who should be administered the beta-blockers treatment. There are certain physicians who claim that all patients suffering from this disease should be administered beta-blockers; there are others who claim that only the patients showing mild symptoms of the disease or those showing no symptoms at all but having a family history and EKG anomalies, while other doctors claim that only the patients with proved symptoms should undergo the beta-blockers treatment.

Congestive (dilated) cardiomyopathy

Having an unknown etiology, it presents high levels of catecholamines in plasma, drawing thus attention on their contribution, since their cardio toxicity is well known, and the patients suffering from congestive

cardiomyopathy might present hyper sensibility due to the decrease of cardiac beta 1 receptors. The reason for using beta-blockers is, therefore, a decrease of catecholamines, respectively their cardiotoxic effect. The decrease of cardiac frequency will lead to a decrease of the myocardial oxygen consumption and a decrease in the number of the cardiac beta 1 receptors.

Beta-blockers, initially administered in small doses, may be benefic for the patients suffering from congestive cardiomyopathy; they improve effort endurance, play a role in the heart size decrease after the remodelling process, increase diastoles and their functions, generate the extension coronary filling time, improve and increase the left ventricle ejection fraction, improve life expectancy by mortality rate decrease etc. These benefic effects of the treatment do not occur instantly but after months of treatment, and improvement may take over 2 years.

The benefit is due to beta 1 blockers and may be associated with the increase of the cardiac beta 1 receptors. Not all patients benefit from this treatment and some of them (often presenting very high levels of plasmatic nor-adrenaline) precipitate cardiac insufficiency or even the state of shock sometimes even when initially administered in small doses, suggesting thus the necessity to select the patients.(4)

Aorta dissection aneurysm

Aorta dissection aneurysm is a major emergency due to the fact that, if untreated, it may lead to death in 90% of the cases, within the first 3 months from dissection. These cases are usually associated to arterial hypertension and thus, the medical treatment is highly important for the decrease of the arterial pressure and velocity reduction of the left ventricular ejection fraction (dp/dt max).

When acute, no matter whether the arterial pressure is high or not, the intra venous administration of the beta-blockers is justified, starting with 0.15 mg/Kg body or the equivalent with other beta-blockers. Blood pressure may be immediately decreased if too high, by the use of a hypotensive agent, such as Na Nitroprusiate.

For distal dissection, the long term treatment is more useful then the surgical treatment, due to a better anti-hypertensive control and a velocity decrease of the left ventricle ejection factor. Because beta 1 blocker is preferable, the choice for the beta-blocker is not so important, except for the cases, where there is a counter indication for beta 2 blockers, such as airways asthma when beta 1 selective agent must be carefully tested.

Life expectancy may thus increase by mortality decrease from 90% in case of untreated patients to 40-50% in patients treated by medical or surgical methods. (5)

Mitral valve prolapse

As a result of a strong emotional state or of anxiety, a hyperkinetic circulation occurs associated with symptoms such as, effort dyspnea, palpitations, exhaustion, *precordial discomfort*, and sometimes tremor with sweating and modified clinical state.

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The symptoms and the clinical state of these patients are similar to the sympathetic super-stimulation, while the hyper-sensibility of the beta-receptors justifies the beta-blockers treatment and has good results. When administered in small doses, they are extremely efficient and diminish or even eliminate the vascular cardiac signs; a non-ISA beta-blocker is recommended.

Orthostatic hypotension

Orthostatic hypotension is one of the most uncomfortable aspects in the patients suffering from chronic autonomous insufficiency. The orthostatic position produces blood accumulation at extremities with a decrease in the central venous pressure, of the cardiac function and of the arterial pressure, a 60° inclination of the body may cause an unconscious fall. These patients present low levels of circulating catecholamines, also presenting high adrenergic hypersensitivity.

Certain patients suffering from mitral valve prolapse also show postural arterial hypotension and cardiac rhythm abnormalities.

The Beta-blockers treatment will cause an increase of the peripheral resistance in the absence of alpha constriction, reducing thus, the postural effects. Beta-blockers with increased ISA activity might cause the continuance or even the increase of the cardiac function; the clinical result varies.

Some authors registered favourable results with Propranolole, others with Pindolol, but there are studies reporting that none of the two beta-blockers is efficient. Newer agents, such as Prenolterol with high ISA, seem to register the best results in small doses, while in larger doses, it might cause precipitation of ventricular arrhythmia, as well as for the beta 1 selective Xamoterol with 43% ISA.(6)

Thyrotoxicosis

Thyrotoxicosis is the result of excessive thyroid hormones secretion, a phenomenon that produces general functional disorder of the body, frequently causing crises resembling to sympathetic super-stimulation. Spontaneous long term remissions occur in 30% of the cases. Propranolole was the beta-blocker most used to remedy certain clinical but also functional aspects; its effects were manifested as an improvement of the clinical state, such as palpitations reduction, an improvement in sweating and in instability. Also, as a result of the Propranolole treatment, there is a metabolic balance of the weight loss cease, cardiac frequency diminishes, but it does not return to normal condition, the increased basic metabolic rate drops, hypercalcemia turns to normal values, serum phosphates increase. Steatorrhea is diminished (although the effect on gastrointestinal transit is disputed), glucose intolerance is improved or even reversed.

Propranolole does not influence (or, if it does, it has a weak influence) the peripheral deiodation process of thyroxin from T₄ to T_a, which leads to T₃ level decrease in serum.

The association of Propranolole with specific therapy may promote the adjustment of the hormonal

disorders unlike the sole Propranolole administration that only improves the clinical signs of hyperthyroidism. Propranolole, administrated with potassium iodide during the preoperative stages is benefic.

The association with the anti-thyroidal agents, during diets, may stop or even cause an involution of goitre and exophthalmia, in doses of 80-240 mg/day but, most importantly, it diminishes the conditions for the occurrence of thyrotoxic crisis.

Subarachnoid hemorrhage

Subarachnoid hemorrhage is a strange clinical syndrome noticed in association with a high secretion of catecholamines and myocardial events. Cardiac sequels include strange anomalies. E.K.G presents focal myocardial necrosis in patients showing high levels of catecholamines. Many of the EKG anomalies may be treated with Propranolole, and the beta-blockers prophylaxis prevents myocardial necrosis induced by catecholamines.

The administration of Propranolole in doses of 3 x 80 mg/day in the first 48 hours from the start of the subarachnoid hemorrhage and afterwards, for three weeks, leads to a significantly lower incidence of complications at central nervous system level, while the one-year follow up will lead to fewer deaths and fewer disability sequels within the group that has been administered the treatment.

The benefits of the treatment with Propranolole are probably due to a lower brain oxygen demand in the patients suffering from brain artery spasms. Atenolol might also be efficient, but there is not enough information in support of these observations.

Serum levels of creatine *phosphokinase* and MB creatine kinase will be normal after 5 days of beta-blockers treatment and patients present a good clinical state.

Patients who are administered placebo with normal creatine *phosphokinase also show good clinical state, unlike the* patients who have been administered placebo but who show high levels of creatine *phosphokinase* and MB creatine kinase maintained during the 5 days of treatment and showing weak clinical results. It is therefore recommended that when there are no counter indications, a beta-blocker like, Propranolole, should be administered within the first 48 hours from the debut of the subarachnoid hemorrhage and then continued for three weeks. In case surgery is planned, the beta-blocker treatment should be administered just a few hours before the surgery and immediately after surgery, postoperative treatment should be administered.

Glaucoma

Primary-open angle glaucoma is the cause for blindness in almost 20% of the blindness cases in USA and is caused by the obstruction of the aqueous humour discharge that leads to the increase of intraocular pressure. Increased production of aqueous humour occurs during ciliary processes that contain ATPase and systems of carbonic *anhydrase* enzymes.

The traditional therapy was based either on

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agents that reduce resistance upon the aqueous humour discharge, such as topic adrenaline and myotics, such as pilocarpine, or on agents that reduce aqueous humour discharge, such as topic adrenaline and carbonic *anhydrase* inhibitors, such as the orally administered acetazolamide. These therapies are nevertheless associated with unpleasant collateral effects. There still are uncertainties about the role of the sympathetic nervous system and of the adrenaline, when dealing with the dynamics of the aqueous humour.

The results obtained in one species cannot always be used in another species and there is an unusual situation in which the intraocular pressure reduction may be the result of stimulation, of alfa-adrenergic blockage, and of alfa-adrenergic stimulation and blockage. The importance of beta 2 receptors in ciliary processes remains uncertain.

The cornea epithelial stratum is the main barrier regarding the beta-blockers penetration in the eye. The most important feature of a beta-blocker, that sets its capacity to penetrate the cornea and to enter the aqueous humour, the ciliary processes and other ocular structures, is the distribution coefficient. Therefore, intense lipophilic beta-blockers, such as Propranolole, penetrate easily while hydrophilic agents, such as Atenolol and Satolol penetrate weakly, and Timolol is placed in an intermediary position.

Most available beta-blockers were showed to reduce intraocular pressure. Oral or topic administrations equally reduce the intraocular pressure. The anaesthetic features of certain beta-blockers make them inoperable because anesthetized cornea is exposed to erosive injuries.

Non-selective beta-blockers with or without intrinsic sympathomimetic activity and beta 1 selective beta-blockers equally reduce intraocular pressure, but hydrophilic blockers that penetrate weakly on the cornea must be topically administrated 3-4 times a day compared to 1-2 times a day for lipophilic beta-blockers, such as Timolol.(7)

Beta-blockers are as efficient as topic adrenaline and myotics, such as pilocarpina and are probably more efficient than acetazolamide. Additive effects appear in beta-blockers, myotics and acetazolamide; as for adrenaline, the situation is a bit blurry. The profile of the collateral effects is more acceptable than the profile of other *antiglaucomatosis* agents. The most common collateral effects when administrating beta-blockers are: local burn after administration, blurry sight, conjunctivitis, dry eyes and punctiform keratitis; these effects are usually transitory but sometimes therapy must be interrupted.

Systemic side effects may occur, such as: bradycardic, cardiac insufficiency, asthmatic effects or side effects of the central nervous system but they are not so unusual.

The ideal *antiglaucomatosis* agent should be long term efficient; for a better compliancy, it should be topically administered 2 times or even once a day, should penetrate the cornea well, should be efficient in small doses and it

should register just few side effects. Timolol is probably the best available agent for the moment.

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