Cardioinhibitors

Cardioinhibitors (drugs that reduce heart activity) act negatively chronotropically (by reducing heart rate) and inotropically (by reducing the contractility of the heart muscle), which leads to a reduction in cardiac output and blood pressure. These changes reduce the activity of the heart and thus the consumption of oxygen by the myocardium. The mechanisms of action of these drugs also include a reduction in electrical conduction (negative dromotropic action).

The mechanical and metabolic effects of these drugs predispose them to the treatment of hypertension, angina pectoris and myocardial infarction. Thanks to their effect on the electrical activity of the heart, they are also suitable for the treatment of cardiac arrhythmias[1]. Some cardioinhibitors (especially certain β-blockers) are used in the treatment of heart failure.

Hypertension

It is caused by an increase in cardiac output or an increase in systemic vascular resistance. Cardioinhibitors decrease heart rate and stroke volume, leading to decreased cardiac output and thus lowering blood pressure.

Angina pectoris and myocardial infarction

Cardioinhibitors (by reducing heart rate, contractility and arterial pressure) reduce the work of the heart and its demands for oxygen. They can thus relieve the patient of anginal pains, which arise most often due to a lack of oxygen during greater exertion. The importance in the treatment of myocardial infarction lies not only in increasing the ratio of oxygen supply and demand, but also in the ability to inhibit post-infarction heart tissue remodeling[1].

Cardiac arrhythmia

Cardioinhibitors alter pacemaker activity and conduction through the heart and are therefore useful in the treatment of arrhythmias caused by both abnormal automation and conduction[1].

Heart failure

Although it may seem paradoxical that cardioinhibitors would be used in heart failure when the myocardium is functionally suppressed, clinical studies have shown that certain cardioinhibitors have been shown to improve heart function in certain types of heart failure[1]. This effect may be derived from their blocking of the excessive sympathetic effects on the heart that damage the failing heart.

Classes of drugs and their general mechanisms of action

Clinically used cardioinhibitors can be divided into three groups: beta-blockers, calcium channel blockers and centrally acting sympatholytics.

Beta-blockers (antagonists of beta-adrenergic receptors)

It binds to **β-adrenergic receptors** in the conduction system and in the working myocardium. Both types are found in the heart: β-1 and β-2 adrenoreceptors. However, β-1 predominates numerically and functionally. These receptors primarily bind noradrenaline released from sympathetic adrenergic nerve endings. It also weighs adrenaline and noradrenaline circulating in the blood. β-Blockers prevent the binding of these ligands to the receptors by competing with them for the binding site. They reduce the effects of the sympathetic (ie, they are sympatholytics) that normally stimulate chronotropy, inotropy, and dromotropic. Their effect even increases if sympathetic activity is increased. Clinically used β-blockers are either **non-selective** (β-1 or β-2) blockers or relatively **selective** β-1-blockers (relative selectivity can be lose the medicine). Some of the β-blockers have other effects besides β-blocking. The third generation of β-blockers are substances that additionally have vasodilating effects by acting on the β-adrenoreceptors of blood vessels.

Some beta-blockers, after binding to the β-adrenoceptor, partially activate while preventing the binding of noradrenaline. These so-called **partial agonists** (partial β-blockers) thus provide a certain background of sympathetic activity, even if they prevent normal or increased sympathetic effects. We speak of them as carriers of their own sympathomimetic activity (***intrinsic sympathomimetic activity, ISA***). Some of the β-blockers are also carriers of membrane stabilizing activity (**MSA**), which is also found in sodium channel blockers belonging to antiarrhythmics.

β-adrenoceptors are coupled to **Gs-proteins** which activate **adenyl cyclase**. The increase in cAMP activates **cAMP-dependent protein kinases** (PK-A), which phosphorylate calcium channels and thus cause increased calcium flux into the cell. The increase in intracellular calcium during action potentials leads to increased release of calcium from the sarcoplasmic reticulum, which ultimately increases inotropy (contractility). Gs-protein activation also leads to an increase in heart rate (chronotropy). PK-A protein kinases also phosphorylate parts of the

sarcoplasmic reticulum, leading to increased calcium release through **ryanodine receptors** (ryanodine-sensitive calcium channels) associated with the sarcoplasmic reticulum. This provides more calcium for its binding to troponin-C, increasing inotropy. PK-A can further phosphorylate myosin light chains, which may contribute to the positive inotropic effect of β-adrenoceptor stimulation. They are used to treat hypertension, angina pectoris, myocardial infarction and arrhythmias[1].

Hypertension

β-blockers lower arterial blood pressure by reducing cardiac output. They can thus represent an effective treatment for hypertension, especially if they are used together with diuretics[1]. In some patients, hypertension is caused by emotional stress, which activates the sympathetic system, in others, for example, pheochromocytoma, which increases the level of circulating catecholamines. Even in these cases, treatment with β-blockers is successful. In addition, β-blockers inhibit the activity of the renin-angiotensin-aldosterone system. Acute treatment with β-blockers is not very effective in lowering blood pressure due to the compensatory increase in vascular resistance in the systemic circulation. The hypotensive effect of the substances of this group is already detectable during the first days of treatment, but they reach their full effect only after 2-3 weeks of administration[2].

Angina pectoris and myocardial infarction

The antianginal effect of β-blockers is attributed to their depressant effect on heart rate, contractility and their hypotensive effects. β-blockers reduce the work of the heart and thereby the need for oxygen saturation of the myocardium (see above).

Cardiac arrhythmia

The antiarrhythmic properties of β-blockers (class II antiarrhythmics) are related to their ability to inhibit the sympathetic influence on cardiac activity. The sympathetic nerve increases the frequency of excitation in the sinuatrial node, which increases the sinus rhythm. Furthermore, it increases the speed of transfer of excitation to the myocardium of the ventricles and stimulates the formation of ectopic excitations. These sympathetic effects are mediated mainly through β-1-adrenoceptors. Therefore, β-blockers may reduce these effects, thereby reducing sinus rhythm, AV conduction velocity (which may block reentry mechanisms), and inhibiting abnormal pacemaker activity. β-Blockers also affect non-pacemaker action potentials by increasing action potential duration and relative refractory period. This effect may play a major role in preventing arrhythmias caused by the reentry phenomenon[1].

Heart failure

Most heart failure patients suffer from systolic dysfunction, i.e. the contractile function of the heart is limited (ie loss of inotropy). Although the mechanism by which β-blockers help in heart failure is not entirely clear, it is certain that they improve heart function and reduce mortality[1].

Classes of β-blockers and specific drugs, clinical use.

Class/Medicine	HTN	Angina	Arrhy	IM	CHF	Comment
Non-selective β-1/2						
carteolol	X					ISA; long acting; also used in glaucoma
carvedilol	X				X	α-blocking effect
labetalol	X	X				ISA, α-blocking effect
nadolol	X	X	X	X		long acting
penbutolol	X	X				ISA
pindolol	X	X				ISA, MSA
propranolol	X	X	X	X		MSA; a typical β-blocker
sotalol			X			yet other effects
timolol	X	X	X	X		yet other effects
β-1-selective						
acebutol	X	X	X		a	ISA
atenolol	X	X	X	X		
betaxolol	X	X	X			MSA
bisoprolol	X	X	X			
esmolol	X		X			especially short effect
metoprolol	X	X	X	X	X	MSA

Abbreviations: HTN - hypertension, Arrhy - arrhythmia, MI - myocardial infarction, CHF - congestive heart failure, ISA - intrinsic sympathomimetic activity

Calcium channel blockers (calcium-channel blockers, CCB)

It binds to **L-type calcium channels** (slow calcium channels[2]) in the cardiomyocyte membrane and nodal tissue. These channels are responsible for regulating the influx of calcium into the myocardial cell, which stimulates its contraction. In cardiac node tissue (SA and AV node), these channels have a role in pacemaker currents and the initial phase of action potential generation. By blocking the entry of calcium into the cell, these drugs act negatively inotropically (reduce the force of cardiac contraction), negatively chronotropically (reduce heart rate) and reduce the speed of impulse transmission through the cardiac conduction system (negatively dromotropically, especially on the AV node). In the smooth muscle of the vessels, they cause relaxation and a decrease in peripheral resistance with a decrease in blood pressure[2]. They are used in the treatment of hypertension, angina pectoris and arrhythmias.

Hypertension

By causing the smooth muscle in the vessel wall to relax, CCBs reduce systemic vascular resistance, thereby lowering blood pressure. These drugs act mainly on arterial resistance vessels, with a minimal effect on venous capacitance vessels[1].

Angina pectoris

The antianginal effects of CCBs are derived from their vasodilatory and cardiac depressant effects. Systemic vasodilatation lowers arterial pressure, which leads to a reduction in ventricular afterload, thereby reducing oxygen demand. The more heart-selective CCBs (verapamil and diltiazem) reduce heart rate and myocardial contractility, making them excellent anti-angiogenic drugs (by reducing myocardial oxygen demand). CCBs can also cause dilation of the coronary arteries, thus preventing their spasm (Prinzmetal's angina pectoris).

Cardiac arrhythmia

The antiarrhythmic group CCB (class IV antiarrhythmics) works mainly by reducing the conduction velocity and prolonging repolarization, especially in the atrioventricular node. Delayed action of the AV node helps prevent the reentry mechanism that can cause supraventricular tachycardia.

Classes of calcium channel blockers

We distinguish three classes of CCB. They differ not only in their basic chemical structure, but also in their relative selectivity to cardiac or vascular calcium channels. Most CCBs acting on vascular smooth muscle are '*dihydropyridines*. They are therefore mainly used to reduce vascular resistance and blood pressure, i.e. to treat hypertension. They are not used to treat angina pectoris, due to their strong vasodilatory and pressure-lowering effect, which can lead to reflex cardiac stimulation (tachycardia and increased inotropy), which leads to a dramatic increase in myocardial oxygen consumption. Dihydropyrinidines include the following specific drugs:

- ***amlodipine***;
- ***felodipine***;
- ***isradipine***;
- ***nicardipine***;
- ***nifedipine***;
- ***nimodipine***;
- ***nitrendipine***.

(note: some newer substances such as amlodipine or isradipine are also called second generation dihydropyridines[2].)

Non-dihydropyridines include two other classes of CCBs. Verapamil (phenylalkylamine class) is relatively selective for the myocardium and is less effective as a systemic vasodilator. This drug is very important in the treatment of angina pectoris and arrhythmias. Diltiazem (benzothiazepine class) is intermediate between verapamil and dihydropyridines in terms of selectivity for vascular calcium channels. It reduces heart rate and has a vasodilating effect. By these mechanisms, it is able to lower blood pressure without causing the same degree of reflex cardiostimulation as the dihydropyridines[1].

Side effects and contraindications

Dihydropyrinidine CCBs can cause congestion, headaches, excessive hypotension, edemas, and reflex tachycardia. From the point of view of activation of sympathetic reflexes and lack of direct effects on the heart muscle, they are not very suitable for the treatment of angina pectoris[1]. Long-acting dihydropyridines have been shown to be safer antihypertensives due to reduced reflex responses. Cardiac-selective non-dihydropyridine CCBs can cause excessive bradycardia, impairment of electrical conduction (AV node block), and decreased contractility. Therefore, they should not be used by patients with chronic bradycardia, cardiac conduction disorders or heart failure. CCBs (mainly non-dihydropyridines) should also not be prescribed to patients who are being treated with β-blockers[1].

Centrally acting sympatholytic

The sympathetic nervous system plays a major role in the regulation of arterial blood pressure. It increases heart rate (positive chronotropic effect), myocardial contractility (positive inotropic effect) and conduction velocity in the heart (positive dromotropic effect). The sympathetic adrenergic fibers that innervate the heart and blood vessels are postganglionic efferent nerve fibers. The cell bodies of these nerves are located in the prevertebral and paravertebral sympathetic ganglia. The sympathetic preganglionic fibers that lead to the ganglia from the spinal cord originate in the medulla oblongata of the brainstem. Sympathetic excitatory neurons are found here, which have a significant basal activity that gives the heart a certain tone under basal conditions. These neuronss receive signals from other, vagal neurons from the nucleus tractus solitarii (receives signals from peripheral baroreceptors and chemoreceptors) and from neurons in the hypothalamus. Together, this neuronal system regulates sympathetic (and parasympathetic) transmission to the heart and blood vessels. Sympatholytic drugs can block the sympathetic adrenergic system at three levels. The first, **peripheral sympatholytics** - antagonists α and β-adrenoceptors – they block the effect of noradrenaline on the effector organ (heart or blood vessels). The other are the so-called *ganglion blockers*, which block the transmission of the impulse in the sympathetic ganglia. The third group consists of drugs that block sympathetic activity inside the brain. We call them *centrally acting sympatholytics*.

Centrally acting sympatholytics block sympathetic activity by binding and activating α2-adrenoceptors in the membrane of medulla cells that regulate cardiac activity. This reduces the sympathetic effect on the heart and cardiac output decreases. These medicines are only used to treat hypertension[1].

Therapeutic indications

Centrally acting α-2-adrenoceptor agonists are used to treat hypertension, but are not used as first-line drugs because of their side effects in the brain. They are usually prescribed in combination with diuretics to prevent fluid build-up that would increase blood volume and thus reduce the effect of the drug. These drugs are suitable for patients with kidney disease, as they do not affect renal function[1].

Specific Medicines

Several different centrally acting antihypertensives are used in clinical practice:

- ***clonidine***;
- ***guanabenz***;
- ***guanfacine***;
- ***α-methyldopa***.

Clonidine, guanabenz and guanfacine are structurally similar drugs and have identical antihypertensive effects. α-methyldopa is a structural analog of dopa and must first be converted to α-methynoradrenaline, which only functions as an α-2-adrenoceptor agonist in the medulla oblongata and reduces sympathetic stimulation. α-Methyldopa is the drug of choice in the treatment of hypertension in pregnancy, when its teratogenicity[1] has not been proven.

Side effects and contraindications

Side effects of centrally acting sympatholytics include sedation, xerostomia, bradycardia, orthostatic hypotension, impotence, and nausea. Swelling may occur during long-term therapy.

Links

Related Articles

- Cardiotonics
- Antiarrhythmics
- Antihypertensives

References

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