Class 4: Calcium Channel Blockers - Antiarrhythmic Drugs

Calcium channel blockers have different scopes of application: they are used for the treatment of arterial hypertension or cardiac arrhythmia. Calcium channel blockers are also applied for the treatment of the coronary heart disease. They are often used if beta blockers cannot be applied due to intolerances or adverse effects.

Overview of Calcium Channel Blockers

The different types

Calcium channel blockers are subdivided into two categories: the dihydropyridines and the non-dihydropyridines. Their main difference is the area at which their effects can be seen. There is no variation in their chemical compositions but they differ in their relative selectivity towards the L type calcium channels.

Dihydropyridines: mainly target system vasculature. So, their activation produces
systemic vasodilation -> decreasing afterload on the heart. This can develop into reflex tachycardia (due to the drop in blood pressure from the systemic vasodilation especially in arteries and the heart’s work to maintain pulse pressure. These drugs include (brand name):

- **Amlodipine** (Norvasc)
- **Nicardipine** (Cardene)
- **Nifedipine** (Nivadil)
- Felodipine (Plendil)
- Nimodipine
- Nitrendipine
- Isradipine

**Note:** Dihydropyridines have names that end in -dipine.

**Non-dihydropyridines:** these are further divided into other groups:

- Phenylalkylamines – Classic example is **Verapamil**. These CaCh blockers mainly act on (selective for) the myocardium itself. They have minimal vasodilatory effects (systemic) and are therefore mainly used to treat angina (where tachycardia would be a bad thing) by reduction of oxygen demand of myocardium and reverse of vasopasm of coronary vessels. It can be also be used to cure arrhythmias.
- Benzothiazepines – Classic example is **Diltiazim** (Cardizem). These are a mix between dihydropyridines and phenylalkylamines. They act as cardiac depressant and vasodialators. They are used to decrease the arterial pressure without causing reflex cardiac stimulation as done by dihydropyridines.
- Nonselective – these mainly relate to the drugs that are nonselective and are able to cross the blood brain barrier.

**Verapamil** predominantly has a direct effect on the heart. **Diltiazem** has an effect on the myocardium as well as peripheral vessels.

**Notice:** Dihydropyridines effect the peripheral vessels, while verapamil acts predominantly at the heart.

**Mechanism of Action**

**The effect on the L-type calcium channel**

Calcium channel blockers **inhibit the voltage-dependent L-type calcium channel** of cardiac and vascular smooth muscle cells. By inhibiting the influx of calcium into the cell, a negative inotropic effect is created and the smooth muscle cells relax and vasodilate.

Dihydropyridines mainly act on vessels (arteries and arterioles), but at high doses will also act on the heart. Therefore, they can **reduce the coronary resistance and vascular resistance** more than verapamil and diltiazem. Verapamil and diltiazem also have a vasodilating effect, but they mainly have a **negative chronotropic and inotropic (it slows it down)** effect at the heart.

The dihydropyridines create a **counter regulation through the sympathetic nervous system**, meaning they can cause an overall increase in heart rate. By decreasing peripheral resistance and blood pressure, the sympathetic nervous system compensates by increasing heart rate.

This effect is rarely seen with diltiazem or verapamil (because they work mainly on the...
heart), instead they have a negative chronotropic effect, slowing down the transition of action potentials at the AV node. Therefore, they are used in antiarrhythmic therapy of atrial fibrillation in order to slow down the ventricular rate.

**Metabolism**

Calcium channel blockers are metabolized by CYP3A4. Rifampicin accelerates the breakdown of calcium channel blockers, whereas antihistamines, protease inhibitors, immunosuppressants, antifungals, and grapefruit juice inhibits the breakdown.

**Adverse Effects**

**Dihydropyridines**

Most common adverse effects include: **headaches, peripheral edemas, excessive hypotension** and **flushing**. An important adverse effect is **reflex tachycardia**, especially associated with nifedipine – which may lead to aggravation of existing heart conditions from to increased cardiac work. Long acting dihydropyridines are safer as antihypertensive drugs and more effective for angina than short acting ones.

**Diltiazem and verapamil**

Most common adverse effects are **bradycardia and type I AV block**. It can also cause depressed contractility. They should not be given with beta blockers as it interfere with action of beta blockers.

**Indications**

**Indications for dihydropyridines**

Dihydropyridines are used for the treatment of **arterial hypertension** as well as **vasospastic angina** (Prinzmetal angina). **Coronary spasms, migraine headaches, Raynaud’s phenomenon** as well as **cerebral vasospasms** and **cerebrovascular insufficiencies** are also treated with dihydropyridines. Substances with a long half-life period, like amlodipine, are preferred for regular use. In contrast, nifedipine only has a half-life period of about 2 hours and hence a short effect duration.

**Note:** Amlodipine has a half-life period of 35-50 hours.

**Indications for diltiazem and verapamil**

Diltiazem and verapamil are used to treat **arterial hypertension**, stable angina, and **hypertrophic obstructive cardiomyopathy**. They are also used as treatment for **supraventricular tachycardia** (they are a type IV antiarrhythmic) and cardiac infarction.

Verapamil has a **distinctive first pass effect**, its bioavailability is only 10-20 % and can also only be increased to 35-40 % during constant use. It is effective in treatment of supraventricular arrhythmias.
Contraindications

Dihydropyridines

Caution should be used in patients with cardiac insufficiency. Contraindications include an acute coronary syndrome (up to 4 weeks after myocardial infarction), persistent bradycardia hypotension, aortic stenosis, or pregnancy.

Diltiazem and verapamil

Contraindications include AV block (grade II and III), sick sinus syndrome, conduction defects and decompensated cardiac insufficiency. Pre-excitation syndromes are also contraindications, especially verapamil because it promotes the occurrence of re-entries. They should not be used in combination with beta blockers as it interferes with action of beta blockers. Diltiazem and verapamil must not be prescribed during pregnancy nor nursing period.

Review Questions

The correct answers can be found below the references.

1. What is the advantage of a therapy with amlodipine compared to the application of other dihydropyridines?
   
   A. Fast onset of action
   B. Longer duration of action
   C. Stronger effects on the AV node
   D. Has an additional effect on the sinus node
   E. Enhanced affinity to L-type calcium channels

2. What is a contraindication for the application of verapamil?
   
   A. Arterial hypertension
   B. Hypertrophic obstructive cardiomyopathy
   C. Angina pectoris
   D. Atrial fibrillation
   E. AV block

3. What belongs least to the adverse effects of dihydropyridines?
   
   A. Flush
   B. Headache
   C. Reflective tachycardia
   D. Re-entry
   E. Peripheral edema

References

Aktories, Klaus u.a.: Allgemeine und spezielle Pharmakologie und Toxikologie, 11. Auflage - Elsevier 2013
ALLEX Alles fürs Examen Band C - Thieme 2012
AMBOSS Medizinwissen
Correct answers: 1B, 2E, 3D

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