

Chapter (9)

Calcium Antagonists

(CALCIUM CHANNEL BLOCKERS)

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- Calcium channel blocking agents (CCB) inhibit the entry of calcium into vascular smooth muscle cells and myocardial cells during the action potential.
- CCBs are a heterogeneous group of drugs with widely variable effects on heart muscle, sinus node function, atrioventricular (AV) conduction, peripheral blood vessels and coronary circulation.
- Classification
 1. *Dihydropyridines (DHP)*
Include: Nifedipine, Amlodipine, Nicardipine, Felodipine, Nisoldipine, Isradipine.
 2. *Nondihydropyridines*
Include:
 - Phenylalkylamines: verapamil.
 - Benzothiazepines: diltiazem

MECHANISM OF ANTI-ISCHEMIC ACTION

1. Increase coronary blood flow

- Decrease coronary vascular resistance- coronary vasodilatation.
- Increase collateral blood flow.
- Decrease coronary spasm.

The most effective in this action is nifedipine

2. Decrease myocardial oxygen demand

- Bradycardia: most effective is verapamil. Nifedipine produces reflex tachycardia.
- Reduction in blood pressure: all members lower blood pressure, the most effective is nifedipine.
- Decrease in myocardial contractility. Most potent is verapamil.

3. Other actions

Decreased platelet aggregation.

DHP calcium antagonists are powerful vasodilators, they possess negligible negative inotropic and electrophysiologic effects. They are ineffective as antiarrhythmic agents.

Verapamil is a moderately potent vasodilator but has a marked negative inotropic effect. It produces mild depression of sinus node function and of AV conduction. It is effective in the termination of AV nodal reentrant tachycardia.

INDICATIONS OF CCBs

1. Stable angina pectoris and acute coronary syndromes.
2. Systemic hypertension.
3. Hypertensive emergencies and perioperative hypertension (IV nicardipine).

4. Treatment and prophylaxis of supraventricular arrhythmias (verapamil, diltiazem).
5. Subarachnoid hemorrhage (nimodipine reduces morbidity and mortality).
6. Hypertrophic cardiomyopathy (verapamil).
7. Primary pulmonary hypertension (diltiazem).
8. Other indications:
 - Amaurosis fugax.
 - High altitude pulmonary oedema.
 - Raynaud's phenomenon.
 - Intracoronary diltiazem or verapamil for no reflow or spasm.

Stable Angina Pectoris

CCBs are used as second line drugs and as effective alternatives or additional drugs in patients who remain symptomatic despite therapy with beta blockers and nitrates. They can be used as first-line antianginal drugs in patients with contraindications to beta blockers.

Coronary Vasospasm and Prinzmetal Angina

- CCBs are drugs of first choice in this syndrome because of their ability to block spontaneous and drug induced spasm.
- Vasospastic angina is characterized by angina usually at rest specially in the morning with ST elevation and usually with preserved exercise capacity. Most patients have some degree of underlying epicardial CAD.
- Coronary spasm and/or thrombosis play a major role in the pathogenesis of ischemia in most patients with angina at rest, regardless of the coronary anatomy.

Unstable Angina

- *Nifedipine* should not be used as a first-line agent but should be used only when B-blockers and nitrate therapy are inadequate for control of ischemia. When combined with BABs, patients receiving nifedipine had a decreased rate of MI and death compared with placebo.
- *Oral diltiazem* is generally safe in patients with unstable angina and is as effective in controlling ischemia as B-blockers. In patients in whom vasospasm is suspected, it is preferable to B-blockers. Diltiazem has been shown to reduce the incidence of infarction or death. Intravenous diltiazem has been shown to be safe and more effective than intravenous nitrates.
- *Verapamil* compares favorably with B-blockers, especially when coronary spasm is suspected. It has not been shown to reduce the incidence of MI or death during short-term follow-up.
- In majority of patients with unstable angina, CCBs have no beneficial effect on mortality or progression of MI but they can be used for the relief of refractory symptoms.

Myocardial Infarction

- Verapamil initiated several days after AMI in patients who were not candidates for B-blockers was useful in reducing reinfarction and death provided LV function is well preserved and no clinical evidence of heart failure.
- Verapamil 360 mg/d started in the second week after AMI and continued for a mean of 16 months reduced major events, but no effect on mortality.
- Diltiazem reduced the frequency of refractory post-infarction angina but no improvement in mortality.
- Verapamil or diltiazem may be a reasonable alternative for patients who can not tolerate B-blockers (severe COPD or asthma).

- Current guidelines recommend the use of verapamil or diltiazem for relief of ongoing ischemia or control of rapid ventricular response with atrial fibrillation after AMI in absence of CHF, LV dysfunction or AV block.

DRUG INTERACTION WITH VERAPAMIL

- *B-Blockers*

Verapamil should not be given as IV bolus to patients receiving B-blockers. It is preferable to give oral preparation.

- *Digoxin*

Verapamil should never be given to digitalized patient when digitalis toxicity is suspected. Serum digoxin levels may be increased by 50 -70 % by verapamil.

- *Amiodarone*

Verapamil is avoided in patients taking amiodarone because of depression of SA and AV nodes.

- *Oral Anticoagulants*

Verapamil increases the effects of oral anticoagulants.

- *Quinidine*

Plasma levels of quinidine may increase during the administration of verapamil. Marked hypotension may develop with IV verapamil.

- *Disopyramide*

Added negative inotropic effect can result in heart failure.

CONTRAINDICATIONS FOR NON-DHP (VERAPAMIL, DILTIAZEM) CCBs

1. Severe impairment of LV systolic function, CHF, or pulmonary oedema.
2. Sinus node dysfunction and AV block (second and third degree).
3. WPW with AF.

Other Contraindications to CCBs

1. Cardiogenic shock.
2. Profound hypotension (SBP < 90 mmHg).
3. Pregnancy and lactation.
4. Significant aortic stenosis.
5. Rapid-release short acting nifedipine must be avoided in the absence of adequate concurrent beta-blockade in acute coronary syndromes.

ADVERSE EFFECTS

Four percent of patients discontinue CCBs because of side effects.

1. Hypotension and dizziness.
2. Oedema of ankles and lower limbs (more common with amlodipine).
3. Headache: more with DHPs.
4. Flushing and burning: more with DHPs.
5. Constipation common with verapamil.

TREATMENT OF DRUG OVERDOSE

- 10% calcium gluconate or calcium chloride.
- Isoprotrenol or dobutamine in severe LV dysfunction or AV block.

DOSAGE: see table 9-1

Table 9-1: Dosage of CCBs

Drug	Usual Dose	Duration of Action
Nifedipine	- Immediate release: 30-90 mg/d - Slow release: 30-180 mg/d	Short (given 3-4 times/d) Short (given 2-3 times/d)
Amlodipine	5-10 mg once daily	Long
Felodipine	5-10 mg once daily	Long
Isradipine	2.5-10 mg Twice daily	Medium
Nicardipine	50 mg BID 20-40 mg 3 times daily	Long Short
Nisoldipine	2-40 mg once daily	-
Nitrendipine	20 mg once or twice daily	Medium
Diltiazem	- Immediate release: 30-80 mg 4 times/d - Slow release: 120-320 mg once or twice/d	Short Long
Verapamil	- Immediate release: 80-160 mg 3 times/d - Slow release: 120-240 mg once or twice/d	Short Long

SOME COMMONLY PRESCRIBED CALCIUM ANTAGONISTS

1. Amlodipine (Norvasc, Amilo, Alkapress)

- It is a DHP derivative with a long duration of action, given once daily.
- It can be given safely to patients with angina and heart failure.
- It does not depress myocardial contractility.
- It has a relatively smooth onset of action; effect starts 2-3 hours after oral administration.
- It is an effective antihypertensive agent.
- Its drawbacks are side effects namely oedema of lower limbs and ankles which can be very inconvenient.

2. Verapamil (Isoptin,)

- It is a non DHP compound.
- It possesses a myocardial depressant action and negative chronotropic effects.
- It slows sinus node activity and A-V node conduction.
- It is particularly useful in patients with angina and sinus tachycardia and can be a good alternative to BABs.
- It has antihypertensive and antiarrhythmic activities.
- Main side effect is constipation.
- Preparations: both immediate release and slow release tablets are available (table 9-1) for oral use. IV preparation is available for rapid control of SVT and AF.

3. Diltiazem (Altiazem, Tildium)

- It is a non DHP compound.
- Actions and indications are similar to verapamil.
- Preparation: both immediate release and slow release tablets. It has a favorable side effect profile, though constipation and ankle oedema may develop.

4. Nifedipine (Epilat, Adalat,)

- It is a DHP derivative.
- It has a potent peripheral and coronary vasodilator action.
- Immediate release form can precipitate sharp fall in blood pressure and reflex tachycardia. This form should be avoided unless the patient is adequately beta blocked.
- Slow release form is effective as both antihypertensive and antianginal agent.
- Common side effects are flushing, headache, palpitation and ankle oedema.
- It is particularly indicated in patients with stable angina and in hypertensive patients who have slow heart rate.
- It has a mild negative inotropic effect.