Calcium Channel Blockers

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- Calcium channel blockers (calcium antagonists; slow channel blockers) block the influx of calcium into various cells, primarily vascular, cardiac, and smooth muscle tissue.
- They are used primarily for treatment of supraventricular tachycardia, angina, and hypertension
- Examples include: amlodipine, diltiazem, felodipine, nicardipine, nifedipine, nimodipine, nisoldipine, verapamil, etc.
- Newer agents include aranidipine, lercanidipine, nilvadipine, nitrendipine, tiapamil.

Mode of Action

All calcium channel blockers (CCBs) act by antagonizing L-type voltage-sensitive slow calcium channels, except mibefradil which blocks T channels. L-channel blockade impairs calcium influx into cardiac and smooth muscle cells, resulting in decreased force of myocardial contraction, negative inotropy, inhibition of SA and AV nodes, and peripheral arteriolar vasodilatation.

Verapamil

- the most powerful myocardial depressant effect
- the most potent at lowering heart rate, cardiac output, and blood pressure

Nifedipine

- weak myocardial depressant
- produces maximum decrease in systemic vascular resistance.

Toxicokinetics & Adverse Effects

- All CCBs are absorbed well orally and are highly protein-bound.
- Verapamil, diltiazem, and nifedipine undergo extensive hepatic metabolism.
- Amlodipine has a very long plasma half-life (35 to 45 hours), and prolonged duration of action.

Adverse Effects

Dizziness, flushing, headache, oedema, palpitations, hypotension, GI upsets. Gingival hyperplasia has been noted with amlodipine.

Drug Interactions

- All calcium antagonists + beta blockers at therapeutic doses and in overdose =Severe bradycardia, conduction blocks and hypotension
- Mibefradil +body's metabolism of lovastatin and simvastatin (and also possibly atorvastatin and cerivastatin)= increase the risk of muscle injury.
- Diltiazem + cisapride = QT interval prolongation
- Verapamil +Erythromycin =Complete AV block and QTc prolongation

Clinical (Toxic) Features

- Early manifestations :dizziness and lethargy. GI manifestations such as vomiting .
- Bradycardia, hypotension,idioventricular rhythms, complete heart-block. Heart rates below 60 beats/min that (asymptomatic patients may subsequently suddenly deteriorate into profound cardiogenic shock)
- Nifedipine and amlodipine lack the effects of other structural classes of CCBs on AV nodal conduction. Therefore, these agents are more likely to result in reflex tachycardia
- verapamil intoxication include heart block, first, second and third degree AV block, junctional rhythm, QT interval prolongation, moderate S-T segment depression, low amplitude T-waves, prominent U-waves, and atrial fibrillation.

- In severe poisoning, convulsions, stroke, renal failure, non-cardiogenic pulmonary oedema, Hyperglycaemia probably because normal calcium influx is impaired by CCBs which affects insulin release from beta cells in the pancreas.
- Acute renal failure usually in patients who develop prolonged hypotension and/or rhabdomyolysis after severe poisoning.
- hypocalcaemia (with tetany) can occur
- . CNS depression, secondary to haemodynamic instability occurs following significant overdose. Effects may include drowsiness, confusion, and coma. Cerebral infarction has been reported. Seizure activity may result from acidosis, anoxia, or an existing predisposition

Treatment

- continuous ECG and haemodynamic status monitoring , electrolytes Monitor, renal function tests and glucose; monitor respiratory function with arterial blood gases.
- Airway protection; oxygenation.
- GI decontamination: stomach wash and activated charcoal. For overdoses involving sustained-release preparations, whole bowel irrigation with polyethylene glycol is said to be beneficial.

- Bradycardia usually responds to atropine, the efficacy of which may be enhanced by initial treatment with calcium.
- Calcium therapy: 10% calcium chloride, or calcium gluconate, While calcium therapy is beneficial in CCB overdose, Use of calcium chloride may aggravate existing acidosis. Calcium therapy is contraindicated in ingestions involving digoxin.
- Hypotension require both fluid replacement, Trendelenburg positioning and vasoconstriction with noradrenaline or high dose dopamine, Calcium may also help

- Glucagon ;It exerts chronotropic and inotropic effects and can help reverse hypotension, but may not improve heart rate.
- Inamrinone, a non-catecholamine inotropic agent has also been used in CCB poisoning with encouraging results. It is usually combined with glucagon or some other inotropic agent such as isoproterenol
- Patients not responding to pharmacologic therapy may require transthoracic or intravenous cardiac pacing. Newer methods include intra-aortic balloon counter pulsation and emergent cardiopulmonary bypass.
- Seizures should be treated with diazepam initially, progressing to phenobarbitone for nonresponsive cases


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