Calcium channel blockers (CCBs) Toxicity

Classification of calcium channel blockers (CCBs):

- **Dihydropyridines (DHP)**
- **Non-DHP**

Mechanism of Action

- CCBs block the inward movement of Ca by binding and blocking the L-type voltage gated Ca channels in the heart and smooth muscles (of peripheral arterioles and coronary arteries) causing dilatation and relaxation mainly of the arterioles.
- All CCBs are therefore vasodilators decreasing arteriolar tone and systemic PVR resulting in decreasing arterial BP (decrease after load).

Mechanism of Action

- In addition CCBs decrease myocardial contractility (-ve inotropic) and heart rate (- chronotropic).
- Diltiazem and verapamil: primary action on heart while dihydropyridines: primary action on arterioles.
- Regarding peripheral Effects: Nefidipine >Diliazem > verapamil while cardiac Effect: verapamil >Diliazem > Nefidipine.

Calcium channel blockers (CCBs) Toxicity

- All CCBs are well-absorbed orally & undergo hepatic oxidative metabolism predominantly via the CYP3A4 subgroup of the cytochrome P450 (CYP) isoenzyme system.
- Norverapamil, formed by N -demethylation of verapamil, is the only active metabolite & retains 20% of the activity of the parent compound.
- Diltiazem is predominantly deacetylated into minimally active deacetyldiltiazem, which is then eliminated via the biliary tract.

Pharmacokinetics & toxicokinetics:

- Saturation metabolism contributes to the prolongation of the apparent half-lives reported following overdose of various CCBs.
- All CCBs are highly protein bound. Volumes of distribution are large for verapamil (5.5 L/kg) & diltiazem (5.3 L/kg), & somewhat smaller for nifedipine (0.8 L/kg).

Pharmacokinetics & toxicokinetics:

- CCBs characterized by their potential for drug–drug interactions. Verapamil & diltiazem specifically compete for CYP3A4 & can decrease the clearance of many drugs including carbamazepine, cisapride, quinidine, (HMG-CoA) reductase inhibitors, cyclosporine, most HIV-protease inhibitors, & theophylline.
- Inhibitors of CYP3A4, such as cimetidine, fluoxetine, some antifungals, macrolide antibiotics, & even the flavonoids in grapefruit juice, raise serum concentrations of several CCBs & may result in toxicity.

Pharmacokinetics & toxicokinetics:

- In addition to affecting CYP3A4, verapamil & diltiazem also inhibit P-glycoprotein–mediated drug transport into peripheral tissue that results in elevated serum concentrations of xenobiotics such as cyclosporine & digoxin that use this transport system.
- Unlike diltiazem & verapamil, nifedipine & the other dihydropyridines do not appear to affect the clearance of other xenobiotics via CYP3A4 or P-glycoprotein–mediated transport.

Clinical manifestations:

- Toxic manifestations of calcium antagonists include
- **myocardial depression**
- **hypotension, syncope**
- **lethargy, dizziness, seizures, and altered mental status**.

Clinical manifestations:

- Specific presentations depend upon the class of calcium channel blocker ingested. For example, during the first 30 minutes of a nifedipine overdose, patients may initially present with tachycardia and normal blood pressure, followed later by hypotension and bradycardia.
- In contrast, patients overdosing on diltiazem or verapamil may present with nausea, vomiting, metabolic acidosis and hyperglycemia (blocks insulin release).

Clinical manifestations:

- The associated clinical findings represent the degree of cardiovascular compromise & hypoperfusion of the central nervous system (CNS).
- Early or mild symptoms include dizziness, fatigue, & lightheadedness, whereas more severely poisoned patients may manifest lethargy, syncope, altered mental status, coma, & death.
- Seizures, cerebral ischemia, ischemic bowel, & renal failure occurring in the presence of CCB-induced cardiogenic shock.

Clinical manifestations:

- Comorbidity & age are two factors that negatively impact both morbidity & mortality in patients with CCBs poisoning.
- Elderly patients, & those with underlying cardiovascular disease such as congestive heart failure, are much more sensitive to the myocardial depressant effects of CCBs.

Clinical manifestations:

- Even at therapeutic doses, these individuals more frequently develop symptoms of mild hypoperfusion, such as dizziness & fatigue.
- One or two tablets of any of the CCBs may produce significant poisoning in toddlers.

Diagnostic testing:

- All patients with suspected CCB ingestions should have continuous cardiac monitoring .
- Careful assessment of the degree of hypoperfusion may include pulse oximetry & serum chemistry analysis for metabolic acidosis.

Diagnostic testing:

- If a patient presents with dysrhythmias of unclear origin, assessment of electrolytes, particularly potassium & magnesium, renal function, & a digoxin concentration, may be helpful, although careful history taking often provides the most valuable clues.
- Acute lung injury can be initially assessed by auscultation, pulse oximetry, & chest radiography.

Management:

- Initial treatment should begin with Adequate airway management because mental status may rapidly deteriorate & aggressive GI decontamination.
- Induced emesis is contraindicated. The most important measures to eliminate CCBs after an ingestion are multiple-dose activated charcoal (MDAC) & , for sustained-release CCBs, whole-bowel irrigation (WBI).

Management:

- Orogastric lavage should be considered for all patients who present early (1 to 2 hours post-ingestion) after large ingestions, & for patients who are critically.
- Pretreatment with a therapeutic dose of atropine is considered. Calcium antagonists are highly protein bound. Therefore, hemodialysis is not likely to be effective at enhancing elimination.

Management:

- All patients ingesting immediate-release preparations should be monitored for a minimum of eight hours after ingestion. Many of the calcium antagonists are available in an extended-release preparation.
- For some of these preparations, onset of action and time to peak concentrations are markedly delayed compared to immediate release preparations. These patients should be observed for 24 hours.

Management:

- Symptomatic patients should be admitted to ICU. An ECG should be obtained upon presentation and repeated frequently (q 1-2 hours for 8 hours) until stable.
- Only asymptomatic patients who have ingested immediate-release preparations and have a normal (or unchanged) ECG at eight hours should be discharged to home.

Management:

- Calcium antagonists affect myocardial contractility and heart rate. Specific therapy is directed to improve contractility, increase heart rate and improve perfusion.

Management:

- For a patient who is hypotensive with no evidence of congestive heart failure or acute lung injury, an initial fluid bolus of 10 to 20 mL/kg of crystalloid should be given, & repeated as needed.
- Atropine is considered the drug of choice for the treatment of symptomatic bradycardia. It may be used initially to increase heart rate in mild to moderate calcium antagonist poisoning, but it is usually ineffective in the treatment of severe calcium channel blocker overdoses.

Management:

- Therapy should begin with crystalloids & atropine, but more critically poisoned patients will not respond to these initial efforts, & inotropes & vasopressors will be needed.
- Although it would be ideal to initiate each therapy individually & monitor the patient's hemodynamic response, in the most critically ill patients, multiple therapies should be administered simultaneously.

Management:

- A reasonable treatment sequence includes calcium followed by a catecholamine such as epinephrine or norepinephrine,-hyperinsulinemia-euglycemia therapy, glucagon, & perhaps a phosphodiesterase inhibitor.

Management:

- Calcium is a logical therapeutic option and is the initial pharmacological agent used by many clinicians. A bolus of 1-2 g (10-20 mL 10%) calcium chloride plus a continuous infusion of 20-40 mg/kg/hr (0.2-0.4 mL/kg/hr 10%) calcium chloride may improve hypotension, conduction abnormalities and cardiac contractility. A continuous infusion is preferred over repeated boluses because sustained increases in extracellular calcium can only be provided through a continuous infusion.

Management:

- Calcium boluses can cause various adverse effects such as nausea, vomiting, confusion, thrombophlebitis, lethargy, cardiac conduction defects with bradycardia and increased oxygen consumption resulting in angina.
- Severe hypercalcemia, although rare, has been reported. Calcium concentrations should be determined every two hours to monitor for hypercalcemia

Management:

- If a cardiac glycoside is a co-ingestant, intracellular calcium may already be elevated and additional calcium may worsen the cardiac glycoside toxicity unless Digibind has been given.
- If a therapeutic benefit is not noted after an adequate trial of calcium, catecholamine therapy should be considered. Dopamine is effective in increasing blood pressure and heart rate, and has been successfully used to treat ingestions of all three classes of calcium channel blockers.

Management:

- An epinephrine continuous infusion may also be effective in improving hemodynamic parameters. Like calcium administration, vasopressors are not always effective.
- Glucagon may improve cardiac contractility and increase heart rate by acting through stimulation of adenylate cyclase and the resultant increase in intracellular concentrations of cyclic adenosine monophosphate (cAMP).

Management:

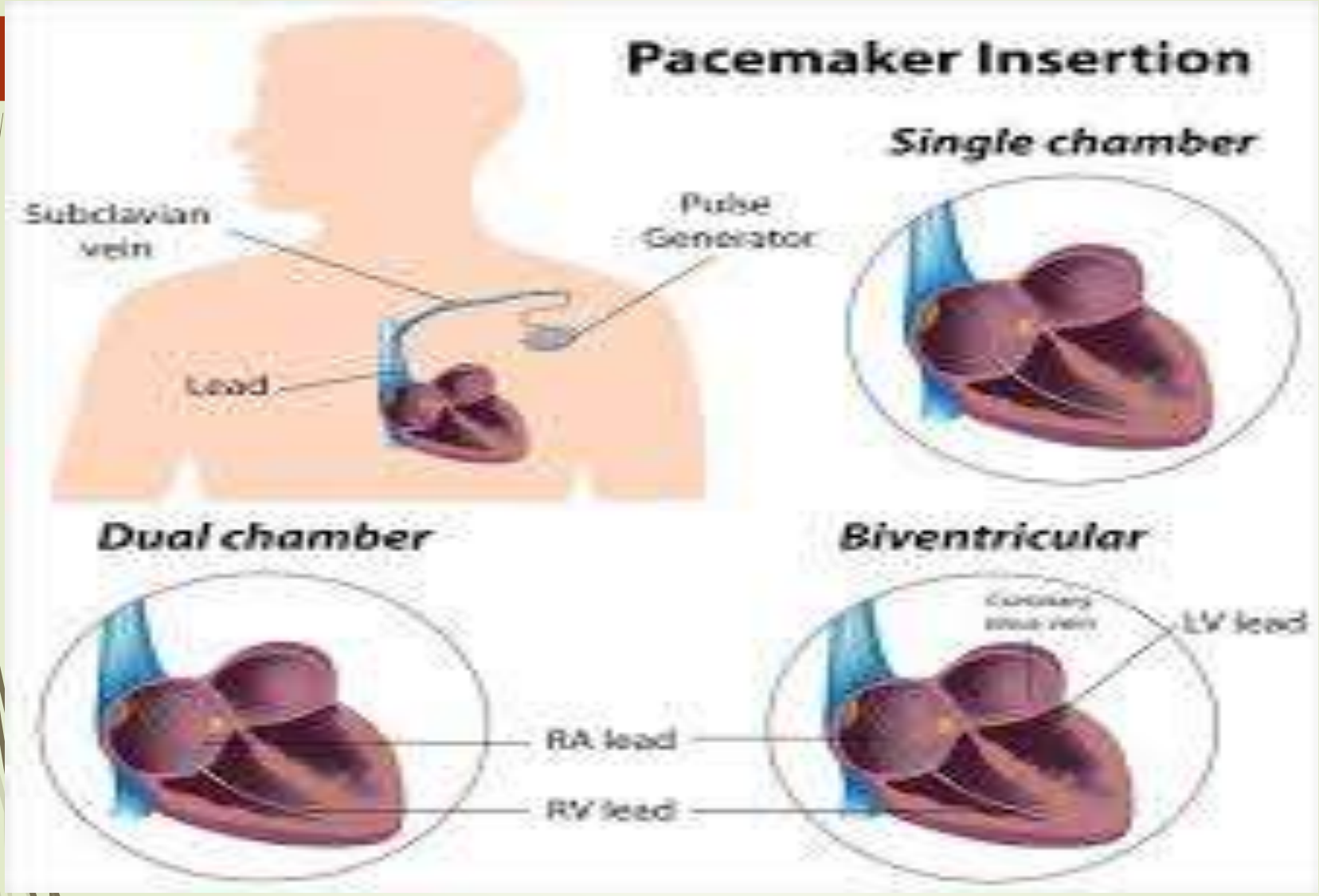
- A reasonable initial dose is 2-5 mg IV over 30-60 seconds for an adult. This may be repeated in five minutes if no response is seen. In preparing glucagon for administration, the diluent provided by the manufacturer should be avoided due to the presence of phenol as a preservative.

Management:

- Another class of therapeutics that is usefulness in treating CCB poisoning is the cardiac & vascular phosphodiesterase 3 inhibitors: inamrinone, milrinone, & enoximone. However, because of the nonselective inhibition of phosphodiesterase 3 by these inhibitors, cyclic adenosine monophosphate (cAMP) is also increased in the vascular smooth muscle. This causes smooth muscle relaxation, peripheral vasodilation & , unfortunately often, hypotension, which may severely limit its usefulness in many CCB-poisoned patients.

Management:

- The most severely CCB-poisoned patients may not respond to any pharmacologic intervention.
- Transthoracic or intravenous cardiac pacing may be required to improve heart rate.
- Newer methods include intra-aortic balloon counterpulsation & emergent cardiopulmonary bypass.


Pacemaker Insertion
Single chamber
Subclavian vein
Pulse Generator
Lead
Dual chamber
Biventricular
RA lead
RV lead
LV lead