Clinical Toxicology

Toxicity of Calcium Channel Blockers

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Objectives of lecture:

Objectives of this lecture are to:

- determine the actions of calcium channel blockers ,
- describe the toxic manifestations of these drugs, &
- determine the management of toxicity.

Classification of calcium channel blockers (CCBs):

- Phenylalkylamine : Verapamil
- Benzothiazepine : Diltiazem
- Dihydropyridines :

  Nifedipine

  Amlodipine

  Felodipine

  Isradipine

  Nicardipine

  Nimodipine

- Verapamil & diltiazem have profound inhibitory effects on the sinoatrial (SA) & atrioventricular (AV) nodal tissue,
- Dihydropyridines as a class have little, if any, direct myocardial effects at therapeutic doses.

Pharmacokinetics & toxicokinetics:

- 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.

- 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).

- One interesting aspect of the pharmacology of CCBs is their potential for drug–drug interactions.

  Verapamil & diltiazem specifically compete for CYP3A4 & can decrease the clearance of many drugs including carbamazepine, cisapride, quinidine, various β-hydroxy-β-methylglutarylcoenzyme A (HMG-CoA) reductase inhibitors, cyclosporine, most HIV-protease inhibitors, & theophylline.

- Inhibitors of CYP3A4, such as cimetidine, fluoxetine, some antifungals, macrolide antibiotics, & even the flavinoids in grapefruit juice, raise serum concentrations of several CCBs & may result in toxicity.
- In addition to affecting CYP3A4, verapamil & diltiazem also inhibit P-glycoprotein–mediated drug transport into peripheral tissue—an inhibition 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.

Physiology & pathophysiology:

- Calcium initiates excitation-contraction coupling & myocardial conduction. In smooth muscle, calcium influx results in contraction.
- Inhibition of L-type-voltage–sensitive calcium channels is particularly significant in the myocardium & smooth muscle, which are dependant on this influx for normal function.

- In the myocardium, this impaired Ca^{2+} flow results in a decreased force of contraction. In addition, the delay in recovery of the slow calcium channels in the SA & AV nodal tissue results in decreased heart rate & conduction.
- In the vascular smooth muscle, any decrease of Ca^{2+} influx results in relaxation & arterial vasodilation.

- In the myocardium, verapamil has the most marked effects, while diltiazem has less & dihydropyridines have little, if any, effect at therapeutic doses.
- In the peripheral vascular tissue, dihydropyridines have the most potent vasodilatory effects; verapamil is the next most potent, followed by diltiazem.

Clinical manifestations:

- Myocardial depression & peripheral vasodilation occur, producing bradycardia & hypotension. Myocardial conduction may be impaired, producing AV conduction abnormalities, & complete heart block.

  The negative inotropic effects may be so profound, particularly with verapamil.

- Hypotension is the most common abnormal vital sign finding following a CCB overdose.

- 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 ischemic events, ischemic bowel, & renal failure occurring in the presence of CCB-induced cardiogenic shock, also are reported.

- Gastrointestinal (GI) symptoms, such as nausea & vomiting, are uncommon.
- The CCB with the most significant myocardial effects, verapamil & , to a lesser extent, diltiazem, are associated with more negative inotropic & chronotropic effects.
- Nifedipine, & likely the other dihydropyridines because of their limited myocardial binding, may produce tachycardia or a “normal” heart rate initially, with bradycardia developing only in patients with more substantial ingestions.

- Numerous reports document hyperglycemia in patients with severe CCB poisoning.
- Acute pulmonary injury is also associated with CCB poisoning.
- Coingestion with other cardioactive xenobiotics, such as β-adrenergic antagonists & digoxin, may potentiate conduction abnormalities.

- 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.

  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, if any, may include pulse oximetry & serum chemistry analysis for metabolic acidosis.
- If a patient presents with bradydysrhythmias 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.
- Measurement of serum glucose concentration.

Management:

- Any patient with a suspected CCB ingestion should be immediately evaluated
- Intravenous access should be initiated.
- Continuous ECG monitoring is needed.
- 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.

- Initial treatment should begin with adequate oxygenation & airway protection (as clinically indicated), & 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).

- Orogastric lavage should be considered for all patients who present early (1 to 2 hours postingestion) after large ingestions, & for patients who are critically.

  Pretreatment with a therapeutic dose of atropine is considered.
- Pharmacotherapy should focus on maintenance or improvement of both cardiac output & peripheral vascular tone.

- Although atropine, calcium, insulin, glucagon, isoproterenol, dopamine, epinephrine, norepinephrine, & phosphodiesterase inhibitors, have been used with reported success in CCB-poisoned patients, no single intervention has consistently demonstrated total efficacy.
- 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.
- A reasonable treatment sequence includes calcium followed by a catecholamine such as epinephrine or norepinephrine, hyperinsulinemia-euglycemia therapy, glucagon, & perhaps a phosphodiesterase inhibitor.

  In addition, in the event of a cardiac arrest, a 20% intravenous fat emulsion may be administered.

- 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.

Atropine:

- Atropine is considered by many to be the drug of choice for patients with symptomatic bradycardia.
- Initial treatment with calcium might improve the efficacy of atropine.

Calcium:

- Calcium ion reverses the negative inotropy, impaired conduction, & hypotension in humans poisoned by CCBs.
- If there is any suspicion that a cardioactive steroid such as digoxin is involved in an overdose, Ca^{2+} should be avoided until after digoxin-specific Fab is administered because of concerns that it may worsen digoxin toxicity.

- The main limitation of using calcium chloride, however, is that it has significant potential for causing tissue injury if extravasated, so administration should ideally be via central venous access.

  Adverse effects of intravenous Ca^{2+}:

  Hypercalcaemia (note: serum calcium should be monitored to prevent hypercalcaemia), nausea, vomiting, flushing, constipation, confusion, & angina.

Inotropes & vasopressors:

- Catecholamines & sympathomimetics such as adrenaline, noradrenaline, dopamine, isoproterenol, & dobutamine have been used with varying degrees of success in CCB poisoning.
- Based on pharmacologic mechanisms, & on experimental data epinephrine, or perhaps norepinephrine, appears to be the most an appropriate initial catecholamine to use in hypotensive CCB-poisoned patients.

- The significant β_1-adrenergic activity of both catecholamines combat the myocardial depressant effects, while the α1-adrenergic agonist effects of norepinephrine (more so than epinephrine) increase peripheral vascular resistance if desired.

Glucagon:

- Glucagon offers no pharmacologic advantage over more traditional β-adrenergic agents.
- There are reports of both successes & failures of glucagon in CCB-poisoned patients who failed to respond to fluids, Ca^{2+}, or dopamine & dobutamine.

Insulin & glucose:

- Hyperinsulinemia euglycemia (HIE) therapy has become the treatment of choice for patients who are severely poisoned by CCBs.
- There are several reported cases of CCB-poisoned patients in whom this therapy successfully improved hemodynamic function mainly by improving contractility, with little effect on heart rate.

Phosphodiesterase inhibitors:

- Another class of therapeutics that has some demonstrated 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.

- Phosphodiesterase inhibitors should be used only as second-line agents, in combination with another inotrope & preferably in patients with hemodynamic monitoring.


Thank
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