# Module 5.2
# Calcium Channel Blockers

## Introduction

Calcium channel blockers (CCB) inhibit voltage activated L-type calcium channels of cell membranes. They have a wide range of clinical applications being used in a variety of disorders such as hypertension, ischaemic heart disease, arrhythmia, migraine and vasospasm.

There are 3 broad classes of calcium channel blockers available:

- Phenyl alkamines (**verapamil**)
- Benzothiapines (**diltiazem**)
- Dihydropyridine (**amlodipine, nifedipine, lercanidipine, felodipine, nimodipine**)

In therapeutic doses, the phenyl alkamines are relatively more cardioselective and the dihydropyridines more vasoselective. The benzothiapines are somewhere in between[1].

## Toxicokinetics

All CCB are well absorbed and undergo significant first pass metabolism. It is possible this first pass effect is saturable resulting in an increased bioavailability in overdose[1]. Peak concentrations are within 1-2 hours for standard release preparations, but can be delayed up to 6 hours. Slow release preparations have variable absorption, with pharmacobezoar formation possible. Peak levels can be delayed for as long as 22 hours.[1]
They are highly protein bound, have large volumes of distribution and are metabolised in the liver. Standard preparations have a relatively short half-life which is why controlled release preparations are available.

## Risk Assessment

Calcium channel blocker overdose can be life-threatening. Verapamil and diltiazem, given their cardio-selectivity have a higher risk profile. Dihydropyridines on their own are much less toxic in overdose. Co-ingestion of agents disrupting the renin-angiotensin axis, such as ACEi or ARBs greatly increase the toxicity and significant vasodilatation can occur. Overdoses with CCBs are associated with significant morbidity and mortality that cannot be predicted by dose alone[2].

Patients often have significant medical comorbidities – prompting the prescription in the first instance. Life threatening arrhythmias have been reported in patients who have ingested as little as 320mg verapamil and 720mg diltiazem[2]. Any paediatric ingestion could be life-threatening.

Cardiovascular toxicity manifests as bradyarrhythmia, myocardial depression and vasodilation. Non-cardiogenic pulmonary oedema has also been reported.
The commonest dysrhythmia in an Australian case series was a junctional bradycardia[2].

Elevated glucose is a marker of toxicity, as insulin release is dependent on calcium channel activation in the pancreas.

## Management

Shock can be multifactorial and treatment should attempt to address the underlying cause. In dihydropyridine toxicity, hypotension generally occurs as a result of vasodilation. Telemetry and echo can help determine the contribution of arrhythmia and poor cardiac contractility to shock. Urgent referral to the Toxicology Unit is necessary. Any acidaemia should be treated aggressively. Ventilation may be required to facilitate intensive therapy.

**To manage bradyarrhythmia**:

- Calcium
- Adrenaline bolus/infusion
- Atropine
- Pacing

**To manage poor cardiac contractility:**

- Calcium
- Adrenaline bolus/infusion
- High dose insulin euglycaemic therapy (HIET)See antidote
- ECMO

**To manage vasodilation:**

- Crystalloid resuscitation
- Noradrenaline infusion
- Vasopressin infusion

**Decontamination**

- Given the potential for life-threatening toxicity, **activated charcoal** should be offered to all patients presenting following CCB overdose, particularly if a slow release preparation is ingested.
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- **Whole bowel irrigation** should be instituted in all but trivial ingestions of slow release preparations, providing toxicity has not already manifested.

**Give 1- 1.5L/h of PEG solution PO or via NGT (GoLytely), (25mL/kg/h if paediatric patient), for up to 5 hours**

### Resuscitation

1. IV fluids, up to 2L
2. A **calcium** infusion should be commenced if there is hypotension.

**Give 10-20mL Calcium chloride 10% as slow push (0.2mL/kg paediatrics) preferably through CVL, while starting infusion 1-10mL/h**

The endpoint should be an ionised calcium of 1.5 - 2.0. Hourly ABGs should be taken initially to monitor adequacy of infusion.

3. If impaired **contractility** is present:
   (i) Commence an **adrenaline** infusion.
   (ii) **HIET**[3] should be commenced if there is ongoing impaired contractility on echo despite >15mcg/min of adrenaline

**Give 1 u/kg bolus of actrapid and commence infusion starting at 100 u/h Titrate q15min aiming for a MAP > 65, (max 10 units/kg/h)**

**Give bolus of 50mL 50% glucose and run 50% glucose infusion at 50mL/h, titrate glucose to achieve euglycaemia**

4. If **vasodilatation** is present:
   (i) Commence a noradrenaline infusion
   (ii) Add vasopressin infusion if ongoing vasodilatation despite >20mcg/min noradrenaline

## Disposition

All patients should be discussed with the Toxicology Unit early. Those exhibiting signs of toxicity will need aggressive intervention and referral to ICU. Those without obvious toxicity may be managed in the SSU with decontamination and ongoing observation. Toxicity with slow release preparations can persist for 48 hours.

## Additional Information

- CCB toxicity is worsened by acidosis. Acidosis should be treated aggressively
- If calcium gluconate is used rather than calcium chloride, 3 times the volume will provide similar elemental calcium. It should also be given as a slow push as rapid injection can worsen hypotension.

- It is possible HIET works through promoting uptake of glucose to the myocardium improving inotropy. HIET results in vasodilation which is likely to require addition of a vasopressor to counteract.

- Significant CNS depression should prompt consideration of co-ingestants.

## Further reading

- Wikitox 2.1.6.1.1 Calcium Channel Blocker http://www.wikitox.org/doku.php?id=wikitox:2.1.6.1.1_calcium_channel_blockers

- Graudins A, Min Lee H and Druda D. "Calcium channel antagonist and beta-blocker overdose: antidotes and adjunct therapies." *Br J Clin Pharm* 81(3):452-61

## References

1. Wikitox 2.1.6.1.1 Calcium Channel Blocker http://www.wikitox.org/doku.php?id=wikitox:2.1.6.1.1_calcium_channel_blockers

2. Howarth D, Dawson A, Smith A, Buckley N and Whyte I. "Calcium channel blocking drug overdose: an Australian series." *Human & Experimental Toxicology* 1994; 13: 161-6

3. Kristin M. Engebretsen, Kathleen M. Kaczmarek, Jenifer Morgan & Joel S. Holger (2011) High-dose insulin therapy in beta-blocker and calcium channel-blocker poisoning, Clinical Toxicology, 49:4, 277-283, DOI: 10.3109/15563650.2011.582471