Calcium Channel Blocker Poisoning
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I. Objectives
1.) Described the classic clinical manifestations of CCB poisoning.
2.) Describe the mechanisms by which CCBs exert their toxic effects in the setting of drug overdose.
3.) Be able to discuss patient disposition for cases of CCB overdose (i.e. when and where should these patients be admitted, how long should they be observed).
4.) Provide appropriate GI decontamination guidelines for the management of CCB overdose patients.
5.) Describe the pharmacological interventions available for the treatment of CCB poisoning, and be able to list them in order of importance or priority.
6.) Understand the mechanisms by which the treatments listed in objective 5 may potentially reverse the toxic effects produced by CCB poisoning.
7.) Describe the appropriate dosing guidelines for the administration of CaCl2 and glucagon in the treatment of CCB poisoning.
8.) Be familiar with how to appropriately monitor a CCB poisoned patient.

II. Introduction

Serious calcium channel blocker (CCB) overdoses are nasty cases to manage often requiring a number of prolonged and aggressive critical care interventions. It is not uncommon for small hospitals to run out of calcium as well as vasopressor and inotropic drugs during the course of managing a CCB poisoned patient. The mortality rate in cases of CCB overdose is one of the highest of all the prescription drugs available in the United States. Only TCAs and opiates are typically associated with more drug-related deaths in the USA, annually. The fact that many of the dispensed CCB drugs are sustained release preparations is also a major contributing factor to the high mortality rate associated with CCB overdose. With overdoses of sustained-release CCB preparation, not only are the patients typically taking extremely large doses of the CCB, the duration is often protracted and wrought with complications requiring relatively long ICU stays. Acute TCA and opiate poisonings are relatively quick in onset and short in duration. An overdose of a sustained release CCB preparation may not display evidence of toxicity for several hours after an ingestion and may last for 24 hours or longer after exposure.

III. Pharmacology/Toxicology

All CCBs bind dihydropyridine (DHP) receptors on cardiac and smooth muscle cell membranes, which inhibits the movement of calcium from extracellular sites through cell membrane-based voltage sensitive L-type calcium channels. This pharmacodynamic action decreases cardiac automaticity and myocardial contractility, and produces dilation of the vascular smooth muscle. Hemodynamic shock with the classic triad of bradycardia, conduction blocks and systemic hypotension are the hallmarks of severe CCB poisoning.

CCBs Four Primary Mechanisms of Toxicity
1) **Dilation of vascular smooth muscle:** Caused by CCB-induced inhibition of the calcium influx. Interference with intracellular binding and release of calcium may also contribute.
2) **Decreased cardiac automaticity:** Calcium entry into SA and AV nodal cells provides the current that results in depolarization. Inhibition of the inward calcium current into myocardial cells slows the heart rate and prolongs AV conduction (PR interval lengthening and bradycardia are seen on EKG).
3) **Decreased myocardial contractility:** Calcium entry during phase 2 of cardiac depolarization triggers release of calcium bound by sarcoplasmic reticulum, which in
turn results in attachment of actin and myosin to cause muscular contraction. CCB’s impede the inward calcium current responsible for triggering contraction and may also affect binding of calcium within the cell.

4) **Impaired carbohydrate utilization:** CCB intoxication is also associated with altered carbohydrate metabolism resulting hyperglycemia, lactic acidosis, and metabolic derangements similar to diabetic ketoacidosis. CCBs shift normal cardiac metabolism away from free fatty acid utilization and forces myocardial cells to become carbohydrate-dependent. Yet, CCBs at the same time prevent adequate myocardial utilization of carbohydrates due to three additional mechanisms of toxicity.

i. CCBs inhibit calcium mediated insulin release by the pancreatic islet cells.
ii. Insulin resistance appears to occur during CCB intoxication
iii. There is poor insulin and substrate delivery due to poor cardiac output.

- This is a vicious cycle in that not only do CCBs directly inhibit myocardial contractility, reduce cardiac output, and reduce peripheral vascular resistance, leading to poor tissue perfusion, but CCBs also impair carbohydrate utilization at the tissue level where carbohydrate utilization is critical during shock.

- CCBs are classified into three major classes with the recent introduction of Bepridil as a new fourth class called a diarylaminopropylamine ether.

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<tr>
<th>CLASS</th>
<th>DRUGS</th>
<th>Pharmacology/Toxicology</th>
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| Phenylalkylamine        | Verapamil  | • May produce profound SA and AV nodal inhibition producing severe cardiac conduction defects.  
|                         |            | • Reduces myocardial contractility.                                                      
|                         |            | • Reduces peripheral vascular resistance but not to the degree of the dyhydropyridines.    
|                         |            | • **Most potent agent at decreasing heart rate, cardiac output, and blood pressure verses the other CCB classes.** |
| Benzothiazepine         | Diltiazem  | • Moderate effects on myocardial contractility and conduction relative to verapamil.     
|                         |            | • Similar effect on vascular smooth muscle when compared to verapamil.                   |
| Dihydropyridines        | Nifedipine, isradipine, amlodipine, felodipine, nimodipine, nicardipine, nisoldipine | • Preferentially binds vascular smooth muscle and predominantly decreases systemic and coronary vascular resistance leading to profound hypotension in the setting of DHP overdose.  
|                         |            | • Produce reflex increases in heart rate at therapeutic levels by the unloading of the baroreceptors.    
|                         |            | • Cardiac contractility and bradycardia may still occur in cases of severe overdose.     |
| Diarylaminopropylamine ether | Bepridil   | • Seldom used; reserved for tx of refractory angina pectoris  
|                         |            | • In addition to calcium blockade, it blocks the fast sodium channels and potassium channels resulting in prolonged QT intervals and potentially ventricular arrhythmias including Torsades de Pointes. |

**IV. Pharmacokinetics**

**Absorption:**

- Rapid GI absorption with the immediate release products with an onset of action of 0.5-3 hours and a duration of action of 6-10 hours.
- Sustained release dosage forms can delay onset and prolong duration of adverse effects. Gastric concretions from SR dosage forms have been found on autopsy. Toxic manifestations of poisoning may begin 1-5 hours after ingestion and may persist for more than 24 hours despite treatment. Rhythm disturbances have been noted up to 7 days after exposure.
Distribution, Metabolism and Elimination

- CCB's are extensively metabolized with very little excreted unchanged in the urine. They are also extensively protein bound in the plasma and have a large volume of distribution making extracorporeal methods of enhanced elimination such as hemodialysis useless.

V. Range of Toxicity

The ‘therapeutic window’ for CCBs is relatively small. Toxic effects may be even be seen in some patients receiving ‘therapeutic’ doses. Any doses greater that the usual therapeutic range should be considered potentially life threatening.

VI. Clinical Manifestations of Toxicity

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<th>Systems</th>
<th>Clinical Effects</th>
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| Cardiovascular | - Severe hypotension is the most common initial clinical finding.  
- Profoundly negative inotropic effects, particularly with verapamil, may alone produce severe cardiogenic shock and death.  
- Junctional escape rhythms are a frequent finding with CCB poisoning. Bradyarrhythmias, AV conduction disturbances, idioventricular rhythms, and complete heart block (AYSTOLE) may occur with all the CCBs, but particularly with verapamil poisoning. |
| Respiratory | Pulmonary edema is frequently attributed to cardiogenic shock, but non-cardiac pulmonary edema has been reported with CCB poisoning in patients with normal left ventricular function. |
| CNS | Cerebral hypoperfusion may produce syncope, lethargy, dizziness, altered mental status, seizures, and coma. |
| GI | Nausea, vomiting, intestinal ileus secondary to vascular hypoperfusion/shock |
| Renal | Oliguria and acute renal failure secondary to vascular hypoperfusion/shock |
| Metabolic | - Hyperglycemia  
- Metabolic acidosis secondary to severe tissue hypoperfusion/shock as well as impaired carbohydrate utilization. |

VII. GI Decontamination

1.) If the patient presents within 2 hours of ingestion, orogastric lavage until returns are clear. Ipecac is not recommended because of the risk of rapid loss of consciousness or abrupt hypotension and cardiac arrhythmias.

2.) **AC: Dose: 50-100 gm (1 gm/kg in kids).**
- Sustained release products warrant repeat doses of AC without the use of a cathartic in the AC. For repeat doses give 1/2 the original dose (0.5gm/kg or 25gm) q3-5 hours x 2 then reassess to determine if additional doses are needed.

3.) Use of whole-bowel irrigation (WBI) should be used for ingestions of sustained-released CCB preparations for the following reasons:
- These drug matrixes are large and poorly removed by lavage.
- Drug matrixes are designed to remain intact in the GI tract for sustained periods of time, and are more rapidly passed with effective use of WBI, thereby reducing the time and extent of absorption of the slowly released calcium channel blocker from the drug matrix.

**Whole Bowel Irrigation**

PEG Dose (polyethylene glycol solution): 1-2 L/h in adults (0.25 to 0.50 L/h in kids) via nasogastric tube until clear rectal effluent.
Antiemetics, preferably ondansetron (Zofran) or ganisetron (Kytril) should be used to control vomiting that invariably occurs with WBI.

VIII. Treatment

1) Airway support, adequate ventilation and oxygenation, IV access, foley catheter.

2) Hypotension
   - The following pharmacological interventions are listed in order of importance for the treatment of CCB poisoning

**Calcium Chloride:**
- Must be considered the **first-line** pharmacologic intervention for the treatment of CCB-induced hypotension.

<table>
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<tr>
<th>CaCl2 Dosing Guidelines for Treatment of CCB-Induced Hypotension</th>
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<tr>
<td><strong>BOLUS DOSE:</strong> 1-2 grams (10-20 ml 10% CaCl2) IV bolus over 5 minutes.</td>
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<tr>
<td>Repeat every 10-20 minutes (as much as 12 grams of CaCl2 over 1.75 hours has been successfully used to treat severe CCB poisoning without the development of significant complications due to hypercalcemia).</td>
</tr>
<tr>
<td><strong>CONTINUOUS IV INFUSION CaCl2:</strong> 20-50 mg/kg/hour</td>
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<tr>
<td>Used in conjunction with bolus dosing of CaCl2 eliminates the occurrence of the large peaks and valleys in systemic calcium concentrations that is associated with bolus dosing and may provide more effective control of CCB-induced cardiotoxicity.</td>
</tr>
<tr>
<td>End-point of CaCl2 therapy is to maintain a serum calcium of 13 to 15 mg/dL, and to reverse the CCB-induced hypotension.</td>
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- Mechanism of action is unclear, but intravenous administration of CaCl2 increases the concentration gradient of calcium across the unblocked calcium channels, allowing for a greater diffusion of calcium intracellularly.
- Many CCB-related deaths have been attributed to inadequate calcium dosing, so it is imperative that aggressive CaCl2 treatment be employed. **Concerns about iatrogenic hypercalcemia should not preclude calcium administration in patients with CCB poisoning.**
- Note that 1 gram of CaCl2 contains equivalent calcium concentration of 3 grams of calcium gluconate, therefore, if **calcium gluconate** is used in the treatment of CCB poisoning, one must administer 3 times the amount of calcium gluconate.
- If there is a suspicion that digoxin poisoning is also involved in an overdose, then calcium must be used very cautiously as it may exacerbate digoxin toxicity unless **Digibind** has already been administered.
**Glucagon:** 2-5 mg IV push (may give up to 10 mg IV push), then 2-5 mg/hour (may titrate up to 10 mg/hr as necessary) in normal saline and titrate as necessary. Do not use the phenol-containing diluent supplied by the manufacturer as it is intended for IM administration.
- Positive inotrope and chronotrope agent that is unaffected by adrenergic depletion or blockade.
- Glucagon circumvents Beta-receptors, and independently stimulates adenyl cyclase, thereby increasing intracellular cAMP which promotes calcium ion influx via calcium channels.
- Administration may exacerbate hyperglycemia and cause vomiting.

**Catecholamines:** If a patient remains hypotensive following CaCl2 and glucagon treatment, then a pulmonary artery catheter should be placed, and the administration of catecholamines (epinephrine 1 mcg/kg per min and titrate) should begin.
- No one single catecholamine has been shown to be superior, but epinephrine is theoretically the best agent because it has potent direct Beta1-adrenergic activity to reverse the myocardial depressant effects and Alpha1-adrenergic effects to increase peripheral vascular resistance.

**Amrinone:** Inotrope which increases intracellular cAMP activity by inhibiting the enzyme phosphodiesterase III. As seen for glucagon, increased cardiocyte cAMP activity increases intracellular calcium, which improves inotropy. However, increase intracellular cAMP activity in vascular smooth muscle produces relaxation, peripheral vasodilation, and reduced systemic vascular resistance, thus potentially exacerbating hypotension. Amrinone must not be considered a first-line agent, and should be used in combination with another vasopressor/inotrope such as epinephrine.

**DOSE:** 1 mg/kg IV bolus over 2 minutes followed by 5 to 20 mcg/kg per minute.

**Hyperinsulinemic Euglycemia**
- (Experimental but very very promising)
- Insulin has positive inotropic effects, and indirect evidence suggests that increased calcium entry may be responsible. Thus, since CCBs poisoning impairs insulin secretion and increases myocardial demand for carbohydrate substrate, treatment with insulin and glucose makes pharmacologic sense.
- Human case studies of severe verapamil poisoning which were refractory to conventional interventions were successfully treated with high dose insulin (mean 0.5 units/kg/hr; range 0.1 to 1.0 units/kg/hr) with concomitant mean dextrose administration of 23.1 gm/hr.

**Non-pharmacologic Interventions**
- Intra-aortic balloon counterpulsation
- Cardiopulmonary bypass
- Extracorporeal membrane oxygenation (ECMO)
3) Arrhythmias

**Asymptomatic:** Supportive measures and ECG monitoring

**Symptomatic:**

**Atropine:** 0.5 to 1.0 mg (0.02 mg/kg in kids) IV every 2 to 3 minutes to a maximum dose of 3 mg.
- Arrhythmias are usually bradyarrhythmias, making atropine the first-line intervention.
- It is not uncommon for CCB-induced bradyarrhythmias to be refractory to atropine therapy.
- Concomitant IV calcium administration may improve the efficacy of atropine therapy.

**Calcium Chloride:** (see dosing guideline provided for the treatment of hypotension)
- Calcium has been reported to help increase sinus rate, and improve AV nodal conduction when used with atropine.
- ACLS guidelines should be followed for the remaining treatment interventions. Intravenous isoproterenol and cardiac pacing will generally follow atropine for the treatment of refractory bradyarrhythmia.

IX. Monitoring/Goals of Therapy

**Patient Disposition**
- Patients who present without signs and symptoms, who have received gastrointestinal decontamination, and whose serial EKGs have remained unchanged after an 8 to 10 hour observation period may be safely discharged to psychiatric care following an 8 to 10 hour observation period.
- Patients ingesting sustained-release products must receive a minimum of 24-hours of ICU observation. Patients presenting with severe signs and symptoms of CCB toxicity should obviously be admitted to an ICU where they can be closely monitored and treated.

- The overall goal of therapy is to restore perfusion to critical organ systems by increasing cardiac output.

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<tr>
<th>Monitor</th>
<th>Goals of therapy</th>
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<tr>
<td>Continuous telemtry with 12-lead EKG every 3 hours</td>
<td>Normal sinus rhythm or return to baseline EKG</td>
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<td>Chem-7 and Magnesium q6-8h initially then q24hrs when the patient is stabilized.</td>
<td>Values within normal limits</td>
</tr>
<tr>
<td>Serum total Calcium, obtain with Chem-7</td>
<td>Reversal of hypotension and conduction disturbances. Calcium concentrations of 13mg/dL or higher may be required.**</td>
</tr>
<tr>
<td>Calcium ionized: Get first level 30 minutes after starting the infusion and every 2 hours thereafter.</td>
<td>Double the baseline ionized calcium</td>
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<tr>
<td>Blood pressure</td>
<td>SBP &gt; 90 mmHg</td>
</tr>
<tr>
<td>HR</td>
<td>&gt; 60 beats/min</td>
</tr>
<tr>
<td>Urine output via foley catheter</td>
<td>1-2 ml/kg/hr</td>
</tr>
<tr>
<td>Mental status changes</td>
<td>A/O x3, Denotes adequate hemodynamic stability.</td>
</tr>
<tr>
<td>Respiratory function: ABG’s, pulse oximeter</td>
<td>ABG’s and oxygenation within normal limits</td>
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**Hypercalcemia:** CCB poisoned patients may typically require large amounts of calcium salt during the course of their intoxication, so close monitoring of serum calcium or ionized calcium is warranted. Fortunately, significant complications due to hypercalcemia are rare. Hantsch et al reportedly administered 12 grams CaCl₂ over 1.75 hours to a critically ill 42 yo female who survived a sustained-release diltiazem overdose. This patient did not display any clinical manifestations of hypercalcemia during the course of her treatment. Her serum calcium after receiving 8 grams of CaCl₂ was 16.3 mg/dL. Many CCB-related deaths have been attributed to inadequate calcium dosing, so it is imperative that aggressive CaCl₂ treatment be employed. *Concerns about iatrogenic hypercalcemia should not preclude calcium administration in patients with CCB poisoning.*

**Signs of hypercalcemia:** Nausea, vomiting, hypertension, shortened QT interval, polyuria, polydipsia, cognitive difficulties, coma, enhanced sensitivity to digitalis and myocardial depression.

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<tr>
<th>Normal Calciums:</th>
<th>mg/dl</th>
<th>mmol/L</th>
<th>meq/L</th>
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<tbody>
<tr>
<td>Total</td>
<td>8.4-10.2</td>
<td>2.1-2.55</td>
<td>4.2-5.1</td>
</tr>
<tr>
<td>Ionized</td>
<td>4.48-4.92</td>
<td>1.12-1.23</td>
<td>2.24-2.46</td>
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Best monitoring methods for patients with severe toxicity are:
1. Early insertion of an arterial catheter to accurately monitor changes in SBP with treatment.
2. Swan-Ganz catheter to monitor pulmonary capillary wedge pressure and cardiac output.

**References**