Target Audience: Emergency Medicine Residents, Medical Students

Primary Learning Objectives:

1. Recognize signs and symptoms of calcium channel blocker toxicity
2. Describe elimination techniques effective for calcium channel blocker toxicity
3. Describe the roles of therapeutic interventions (e.g. glucagon, calcium, high-dose insulin, intravenous lipid emulsion, etc.) in the patient with calcium channel blocker toxicity
4. Discuss the indications, contraindications, and efficacy of transcutaneous and transvenous pacing in the patient with symptomatic bradycardia from presumed but undifferentiated toxic exposure (e.g. calcium channel blocker, beta-blocker, digoxin, etc.)

Secondary Learning Objectives: detailed technical/behavioral goals, didactic points

1. Describe the pathophysiology of calcium channel blocker toxicity
2. Compare the differences and similarities in presentation, diagnosis, and management in toxic overdoses causing symptomatic bradycardia (calcium channel blockers, beta-blockers, digoxin, etc.)
3. Discuss the management priorities for the emergent stabilization of the patient with calcium channel blocker toxicity
4. Describe the methods used to minimize absorption and enhance elimination of toxic calcium channel blocker ingestions.

Critical actions checklist:

1. Obtain IV access. At least two large bore IVs needed initially, then central venous access.
2. Give maximal cardiovascular support to include standard measures for hypotension and high-dose insulin and glucose therapy.
3. Obtain ECG and correctly interpret first-degree AVB with bradycardia.
4. Consult Toxicology.
5. Rule out co-ingestants (i.e., ASA, APAP) (assess by obtaining collateral history and ordering lab tests).
6. Admit to the ICU.

Environment:

1. Room Set Up – ED critical care area
    a. Manikin Set Up – Mid or high fidelity simulator, simulated sweat
    b. Props – Standard ED equipment

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CASE SUMMARY

SYNOPSIS OF CASE

The setting is an urban emergency department.

Patient is a 56-year-old man with a history of hypertension and depression who is delivered to the emergency department by EMS following an intentional ingestion of verapamil (both immediate and extended-release). The medics have given the patient a dose of 50g activated charcoal (AC) in the field. On arrival, he is awake, alert, and oriented, though with mild hypotension and bradycardia. The patient will quickly become hemodynamically unstable. Orogastric lavage will not be available. He will remain hemodynamically unstable throughout the majority of the case.

SYNOPSIS OF HISTORY

Mr. Blue is a 56-year-old man who has battled depression for years. His doctors recently switched his anti-hypertensive therapy from immediate acting verapamil to sustained release verapamil, though he never disposed of the old medication. He recently lost his job and is now facing divorce. Approximately 45 minutes before summoning EMS himself, he took “all” his verapamil. There was no co-ingestion with other medications, drugs or alcohol. He will have arrived to the ED approximately 60 minutes after his ingestion.

SYNOPSIS OF PHYSICAL

Per EMS personnel, he is awake and oriented. Field vital signs are: BP 95/50, HR 55, RR 16, SaO2 98% RA. On arrival to the ED, BP is 92/48, HR 52, RR 18 and SaO2 97%. He is awake, alert, oriented. His physical exam is unremarkable initially. However, over the next several minutes, his BP/HR will become significantly worse and he will become diaphoretic. The patient will maintain his airway, but with GCS 10-12. If time allows, and the leader has appropriately managed the cardiovascular instability (which is the focus of the simulation), the examiner may make the patient obtunded and therefore, prompt endotracheal intubation.

SCORING GUIDELINES

The team leader needs to be aggressive with cardiovascular support and team management. Score up for timely use of fluids, pressors, and high-dose insulin/glucose[1] therapy. Orogastric lavage will not be available. Score down if the team leader does not quickly request Toxicology consultation. Further GI decontamination is at the discretion of the team leader and consulting toxicologist. Central IV access will be needed before initiating pressors. Intravenous lipid emulsion therapy may be considered. Transvenous pacemaker may be considered, but is not necessary, and will not work.

[1] High dose insulin-euglycemia therapy (HIE)

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CRITICAL ACTIONS

1. **Obtain IV access.**

   Obtain IV access. Initially, learner should order the insertion of at least two large-bore (greater than 20 gauge) peripheral venous catheters. As the case progresses, central venous access will be preferred.
   Cueing Guideline: Nurse can ask if the doctor would like venous access established.

2. **Optimize cardiovascular status.**

   Initially, learner should provide empiric interventions for hypotension and bradycardia until the actual etiology is elicited. These empiric interventions may include IV crystalloid fluid boluses, atropine, calcium, glucagon, and attempts at pacing (no effect will be seen with these interventions). As the case progresses and the actual etiology for the patient's symptoms are discovered, central venous access will be needed, and additional calcium, high-dose insulin/glucose therapy, intravenous lipid emulsion, and other interventions may be provided.
   Cueing Guideline: Nurse can prompt the doctor as initial empiric interventions are attempted without effect or clinical improvement.

3. **Obtain ECG.**

   Obtain ECG. Correctly interpret findings (first-degree AV block with bradycardia).
   Cueing Guideline: The nurse can ask if the doctor would like an ECG (this prompt can be delivered if the learner requests that the patient be placed on continuous telemetric monitoring).

4. **Rule-out co-ingestants.**

   Exclude other co-ingestants like acetaminophen and aspirin. The learner fulfills this critical action by obtaining collateral history and ordering the appropriate lab tests.
   Cueing Guideline: The nurse can ask if the doctor would like additional diagnostic tests to help rule-in or rule-out possible etiologies for the patient's symptoms.

5. **Consult Toxicology.**

   Consult Toxicology.
   Cueing Guideline: RN can ask the doctor if anyone has called the Toxicologist yet. RN may also ask if there is anything more we can do to help improve the patient's condition and (if the etiology is known) eliminate or neutralize the calcium channel blocker.

6. **Admit to the ICU.**

   Admit to the ICU. Patient will not be stable for any other destination.
   Cueing Guideline: RN can ask the doctor if anyone has called the intensivist to arrange for a definitive disposition decision.

Critical Actions Checklist[2]

Resident Name	
Case Description	

Skills measured **Core competencies: PC** Patient care, **MK** Medical knowledge, **IC** Interpersonal and communication skills **P** Professionalism, **PB** Practice-based learning and improvement **SB** Systems-based practice	Very Unacceptable		Unacceptable		Acceptable		Very Acceptable	
Data Acquisition (D) PC MK I	1	2	3	4	5	6	7	8
Problem Solving (S) PC MK PB	1	2	3	4	5	6	7	8
Patient Management (M) PC MK IC P PB SB	1	2	3	4	5	6	7	8
Resource Utilization (R) PC PB SB	1	2	3	4	5	6	7	8
Health Care Provided (H) PC SB	1	2	3	4	5	6	7	8
Interpersonal Relations (I) IC P	1	2	3	4	5	6	7	8
Comprehension of Pathophysiology (P) MK PB	1	2	3	4	5	6	7	8
Clinical Competence (C) PC MK IC P PB SB	1	2	3	4	5	6	7	8

Critical Actions

Yes	No		Comments:
		Obtain IV access (must include peripheral and central venous access).	
		Administer IV fluid boluses.	
		Optimize cardiovascular status (must include insulin/glucose)	
		Obtain ECG.	
		Consult toxicology.	
		Rule-out other co-ingestants.	
		Admit to the ICU.	

Yes	No	
		Dangerous actions

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[2] Modified ABEM Oral Certification Examination checklist and scoresheet

HISTORY

You are called to see a new patient who presents to the emergency department following an intentional ingestion of verapamil. He appears awake, alert, and slightly mottled.

Age: 56

Sex: Male

Name: Mr. Blue

Method of Transportation: Ambulance

Person giving information: Patient

Background Info: Mr. Blue ingested “all” of his verapamil tablets approximately 45 min before calling EMS. He felt remorseful for his actions and wanted to get help.

Chief Complaint: Intentional Verapamil Overdose

Past Medical Hx:
1. Depression
2. Hypertension

Habits: No smoking, no drugs, occasional alcohol use.
Loves pina coladas and getting caught in the rain.

Family Med Hx: Non-contributory

Social Hx: Married, but separated and facing imminent divorce.
Two children, both out of state in college.
Lives two miles away from hospital.

Medications:
1. Verapamil SR 240 mg daily (current medication).
2. Verapamil 120 mg BID (old medication).

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PLAY OF CASE GUIDELINES

The patient took “all” of his verapamil tablets. He will not remember how many he took, but states “it was a couple handfuls.” This case is intended to be one of a markedly unstable patient. With calcium channel blocker overdoses, patients frequently deteriorate despite appropriate, timely management. The goal is to test the ability of the team leader to guide his team through this clinical deterioration, and quickly escalate therapy using all of the medications/interventions in his/her armamentarium. This case is not intended to be a diagnostic dilemma.

1. The patient will quickly become hemodynamically unstable. A second IV is needed on arrival. If it is not requested, the first line will infiltrate and be unusable.

2. OG lavage is not available.

3. Any of the standard ACLS therapies for hypotension and or bradycardia are acceptable interventions. It is expected that the patient will remain unstable as the team continues to escalate cardiovascular support. If the patient does not receive high-dose insulin/euglycemia therapy (HIE), he will worsen. If the examiner feels that the leader is not rapidly progressing through therapies, the patient will have a brady-systolic arrest.

4. If the patient is not intubated if/when he becomes obtunded, he will become hypoxic and code.

5. If Toxicology is not consulted before MICU admission is attempted, MICU will refuse admission.

6. If a pharmacist is available, he/she should be preparing medications.

7. The transcutaneous pacemaker will be available for the case, but will not be effective. If the leader does not recognize this quickly (i.e., after maximal current fails to result in capture), he/she will need to be prompted to move along. The transvenous pacemaker is not available.

Required Actions within the First Two Minutes

- Point-of-care glucose ordered
- Peripheral IV access ordered/inserted
- ABG/VBG, electrolytes, other diagnostics, and ECG are ordered
- Initial (empiric) interventions for symptomatic bradycardia and hypotension of unspecified etiology (until history of calcium channel blocker ingestion acquired)

Branch Points

- **IF NO POINT-OF-CARE GLUCOSE IS ORDERED WITHIN THE FIRST TWO MINUTES,** patient becomes more confused and obtunded.
- **INITIAL EMPIRIC INTERVENTIONS DIRECTED AT CCB TOXICITY WILL HAVE NO RESPONSE;** patient will progressively deteriorate without high-dose insulin/glucose therapy, intravenous lipid emulsion therapy, and toxicology consultation.
- **NURSE MAY PROMPT FOR THE ABG/VBG, ELECTROLYTES, OTHER DIAGNOSTICS, and ECG** if they are not ordered by this time.

Required Actions over the Next Four Minutes

- Peripheral IV infiltrates/becomes unusable; patient requires central venous access
- Vasopressors, high-dose insulin/glucose therapy, intravenous lipid emulsion therapy, and toxicology consultations should be ordered
- MICU consultation for definitive disposition and placement

Branch Points

- **PATIENT WILL PROGRESSIVELY DETERIORATE WITHOUT HIGH-DOSE INSULIN/GLUCOSE THERAPY, INTRAVENOUS LIPID EMULSION THERAPY, AND TOXICOLOGY CONSULTATION.** Failure to recognize the need for central venous access, these more specific interventions, and consultation will result in progressive worsening of the patient's status and cardiac arrest/respiratory failure.

- **NURSE MAY PROMPT FOR THE MICU CONSULTATION** if not already requested.

Required Actions over the Remainder of the Case

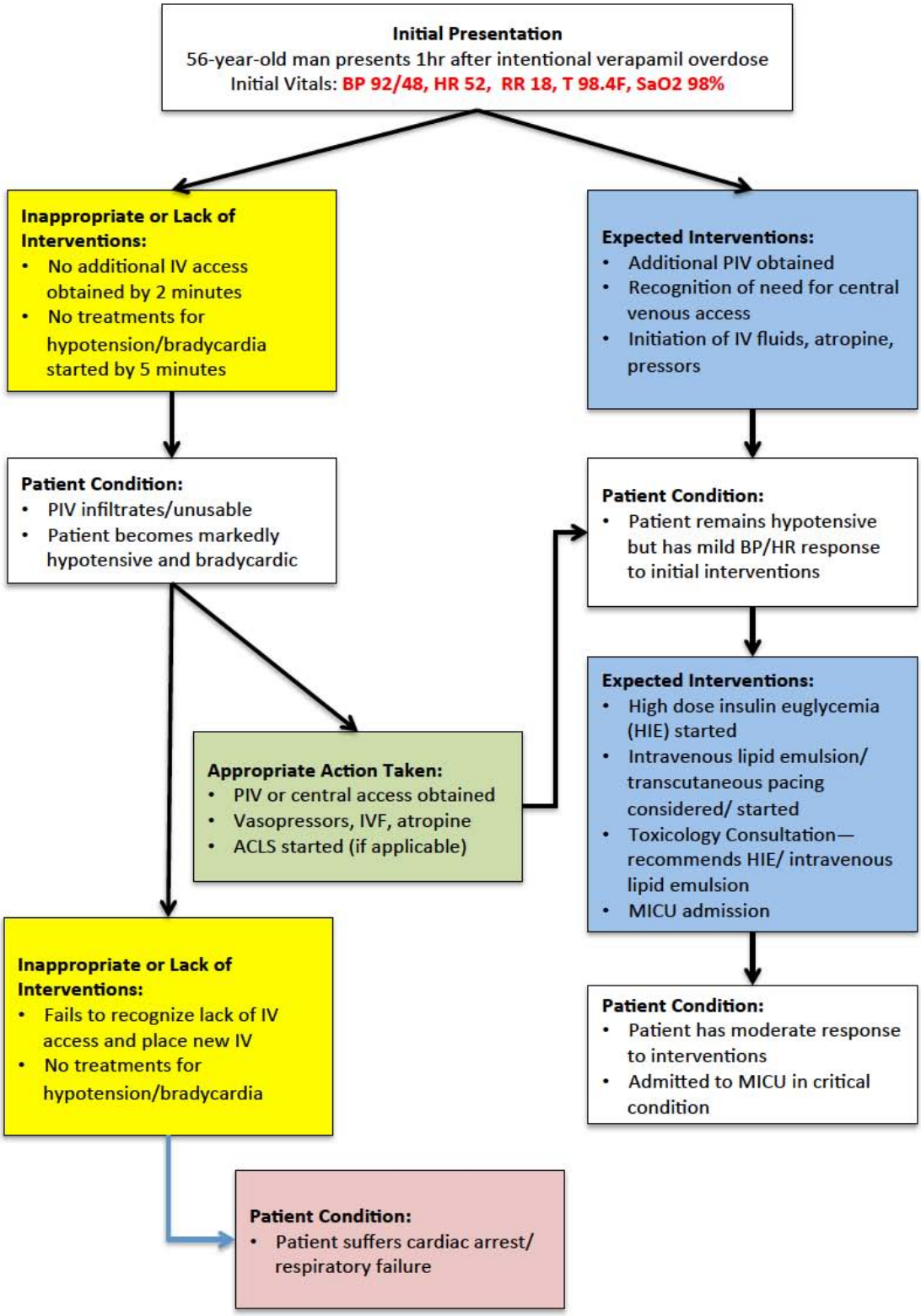
- Central venous access should be achieved by this time
- Vasopressors, high-dose insulin/glucose therapy, intravenous lipid emulsion therapy, and toxicology consultations should be started, and moderate response and clinical improvement should be noted
- MICU consultation for definitive disposition and placement
- Consultation with the Medical Intensive Care Unit for admission

Branch Points

- **PATIENT WILL PROGRESSIVELY DETERIORATE WITHOUT HIGH-DOSE INSULIN/GLUCOSE THERAPY, INTRAVENOUS LIPID EMULSION THERAPY, AND TOXICOLOGY CONSULTATION.** Failure to recognize the need for central venous access, these more specific interventions, and consultation will result in progressive worsening of the patient's status and cardiac arrest/respiratory failure.

- **NURSE MAY PROMPT FOR THE MICU CONSULTATION** if not already requested.

Timeline and Branch Points for This Case



PHYSICAL EXAM

General Appearance: Awake, alert, slightly mottled

Vital Signs: **BP: 92/48 mmHg P: 52/minute R: 18/minute T: 37C (98.7F) POx: 98%**

HEENT: PERRLA, 4mm, moist mucous membranes, remainder unremarkable.

Lungs: Clear.

CV: Bradycardic, weak, but palpable pulses.

Abdomen: Soft, non-tender. Active BS. Non-distended.

Extremities: Cool, slightly mottled. Atraumatic.

Rectal: Heme negative.

Back: Atraumatic.

Neurological: Awake, alert initially. With time, mental status deteriorates slightly, GCS 10-12. Moves all extremities equally. No focal deficits.

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STIMULUS INVENTORY

#1	Complete blood count
#2	Basic metabolic panel
#3	Urinalysis
#4	Liver function tests
#5	Arterial blood gas
#6	Creatinine phosphokinase
#7	Toxicology
#8	Coagulation studies
#9	Serum glucose
#10	ECG

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LAB DATA & IMAGING RESULTS

Stimulus #1	
Complete Blood Count (CBC)	
WBC	12,000/mm^3
Hemoglobin	12.5 g/dL
Hematocrit	36%
Platelets	115,000/mm^3
Differential	
PMNLs	80%
Lymphocytes	9%
Monocytes	7%
Eosinophils	4%

Stimulus #2	
Basic Metabolic Profile (BMP)	
Sodium	135mEq/L
Potassium	3.0mEq/L
Chloride	104 mEq/L
Bicarbonate	20 mEq/L
Glucose	262 mg/dL
BUN	25 mg/dL
Creatinine	1.1 mg/dL

Stimulus #3	
Urinalysis	
Color	Yellow
Specific gravity	1.030
Glucose	Negative
Protein	Negative
Ketones	Negative
Leuk. Esterase	Negative
Nitrites	Negative
WBC	0-2/hpf
RBC	0-2/hpf

Stimulus #4	
Liver Function Tests	
AST	35 U/L
ALT	38 U/L
Alk Phos	60 U/L
T. Bilirubin	0.8 mg/dL
Albumin	4 mg/dL
Protein	7 mg/dL

Stimulus #5	
Arterial Blood Gas	
pH	7.34
pCO_2	34 mm Hg
pO_2	90 mm Hg
HCO_3	20 mEq/L
SaO_2	97% (FiO_2=0.21)

Stimulus #6	
Creatine phosphokinase	
CPK	80 U/L

Stimulus #7	
Toxicology	
Salicylate	< 4 mg/dL
Acetaminophen	< 10 mcg/mL
Ethanol	Undetectable
Urine drug screen	
Amphetamines	Negative
Benzodiazepines	Negative
Cocaine	Negative
Opiates	Negative
TCAs	Negative
THC	Negative

Stimulus #8	
Coagulation Studies	
INR	1.0
PTT	32 seconds

Stimulus #9
Serum glucose
250 mg/dL

Stimulus #10
ECG

Stimulus #1

Complete Blood Count (CBC)

WBC	12,000/mm^3
Hemoglobin	12.5 g/dL
Hematocrit	36%
Platelets	115,000/mm^3
Differential	
PMNLs	80%
Lymphocytes	9%
Monocytes	7%
Eosinophils	4%

Stimulus #2

Basic Metabolic Profile (BMP)

Sodium	135mEq/L
Potassium	3.0mEq/L
Chloride	104 mEq/L
Bicarbonate	20 mEq/L
Glucose	262 mg/dL
BUN	25 mg/dL
Creatinine	1.1 mg/dL

Stimulus #3

Urinalysis

Color	Yellow
Specific gravity	1.030
Glucose	Negative
Protein	Negative
Ketones	Negative
Leuk. Esterase	Negative
Nitrites	Negative
WBC	0-2/hpf
RBC	0-2/hpf

Stimulus #4

Liver Function Tests

AST	35 U/L
ALT	38 U/L
Alk Phos	60 U/L
T. Bilirubin	0.8 mg/dL
Albumin	4 mg/dL
Protein	7 mg/dL

Stimulus #5

Arterial Blood Gas

pH	7.34
pCO_2	34 mm Hg
pO_2	90 mm Hg
HCO_3	20 mEq/L
SaO_2	97% (FiO_2=0.21)

Stimulus #6

Creatine phosphokinase

CPK	80 U/L

Stimulus #7

Toxicology

Salicylate	< 4 mg/dL
Acetaminophen	< 10 mcg/mL
Ethanol	Undetectable
Urine drug screen	
Amphetamines	Negative
Benzodiazepines	Negative
Cocaine	Negative
Opiates	Negative
TCAs	Negative
THC	Negative

Stimulus #8

Coagulation Studies

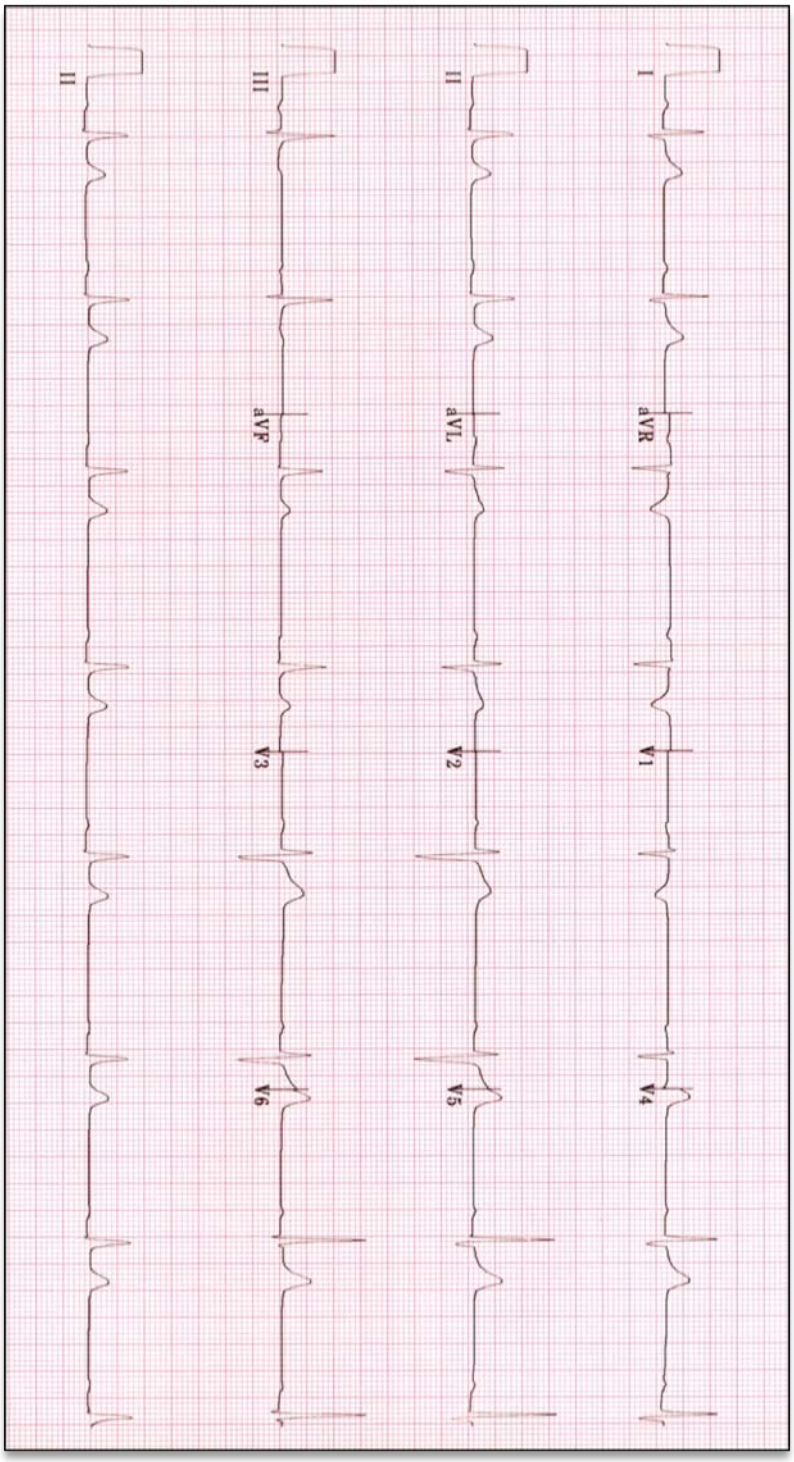
INR	1.0
PTT	32 seconds

Stimulus #9

Serum glucose

250 mg/dL

Stimulus #10



Teaching Points: Calcium Channel Blocker Toxicity

Risk Assessment:

1) Drug: Verapamil and Diltiazem commonly cause cardiovascular collapse in OD and have delayed effects (4-16 hours after ingestion) with slow release (SR) or sustained release preparations.
2) Dose:
    a. Ingestion of > 10 tablets of verapamil SR or diltiazem SR in an adult may cause serious toxicity. All deliberate self-poisonings are potentially lethal.
    b. Onset of effects occurs w/I 2 hours post ingestion for immediate release and 16 hours for sustained release tablets.
    c. Other CCBs usually do NOT cause life-threatening toxicity regardless of dose.
    d. Coingestion of other cardiotoxic drugs increases the risk of serious toxicity.
3) Patient:
    a. Advanced age and comorbidities increase the risk of toxicity.
    b. Children: Ingestion of 1-2 tablets of verapamil SR or diltiazem SR is potentially lethal.

Uses: Calcium Channel Blockers (CCB's) are used in the treatment of angina pectoris, coronary artery spasm, hypertension, hypertrophic cardiomyopathy, Raynaud's, high-altitude pulmonary edema, congestive heart failure, supraventricular dysrhythmias, and migraine headaches.

Mechanism of toxicity: CCB block the passage of calcium into cells by slowing the movement of calcium through the L-type slow voltage gated calcium channels on cardiac myocytes, cardiac conduction tissue, vascular smooth muscle, and pancreatic beta cells. Calcium influx augments actin-myosin binding in both cardiac and smooth muscle cells resulting in increased inotropy and arterial tone. Insulin release from pancreatic beta cells is calcium mediated. Blockade of these channels results in coronary and peripheral vasodilation, reduced cardiac contractility, slowed AV node conduction, decreased sinus node activity, and hyperglycemia.

There are three chemical classes available which can lead to markedly different clinical effects when used therapeutically, depending on the affinity of the drug for different L-type calcium channels. This selectivity may be lost in overdose.

1) Phenylalkylamine class—Verapamil (Covera HS, Calan) has its greatest effect at the SA and AV nodes resulting in decreased heart rate, blood pressure, and cardiac output.
2) Dihydropyridine class—Nifedipine (Procardia), Amlodipine (Norvasc), Felodipine (Plendil), Nicardipine (Cardene), Nimodipine (Nimotap), have their greatest effects on the peripheral vascular smooth muscle cells and little affinity for myocardial calcium channels resulting in the largest decrease in systemic vascular resistance. These may present with vasodilation, but in overdose myocardial depression is possible.
3) Benzothiazepine class—Diltiazem (Cardizem) has moderate affinity for both myocardial and peripheral calcium channels resulting in intermediate effects.

Pharmacokinetics: Well absorbed orally. Rapid onset (1-2 hours) for regular preparations, and may be delayed in sustained release formulations. Highly protein bound with large volumes of distribution, so hemodialysis is ineffective. Elimination is via hepatic metabolism with potential for drug interactions.

Toxic Dose: The therapeutic window is small, and any dose above the therapeutic range should be considered potentially toxic. Sustained release preparations may present late or

result in prolonged toxicity. Lowest reported doses resulting in death in case reports: Amlodipine (70 mg), Nifedipine (200 mg), Verapamil (1.4 g), and Diltiazem (720 mg).

Clinical presentation**:**
Cardiac:

1) Hypotension: caused by peripheral vasodilation, reduced heart rate, decreased contractility, or any combination of the three.
2) Bradycardia: with sinus depression, any AV block, or sinus arrest with a junctional arrhythmia.

Non-cardiac:

1) CNS: Nausea/ vomiting, dizziness, altered mental status, seizure (depending on the severity of hypoperfusion, but AMS and seizure do not occur without hypoperfusion).
2) Metabolic acidosis may occur from hypoperfusion.
3) Hyperglycemia resulting from decreased insulin release.
4) Acute lung injury/ARDS is possible as well.

Decontamination and Enhanced Elimination:

1) Charcoal – Charcoal binds CCB's. Administer charcoal if the patient has an intact airway. If patient is intubated, place an OGT and give AC.
2) Multi-dose charcoal – Should be considered in the setting of a large overdose or sustained-release preparations of CCB's.
3) Gastric lavage – Should be considered for the patient who presents early with a massive overdose, as these patients are at a high risk for hypotension and cardiac dysrhythmias. Reducing absorption of the drug may prevent these sequelae. There is a theoretical concern for increasing vagal tone and worsening bradycardia.
4) Whole bowel irrigation – Should be considered with sustained release preparations.
5) Hemodialysis – Due to extensive protein binding CCB's are not effectively removed by hemodialysis.

Treatment:
Supportive measures: Maintain airway and ventilation. Volume replacement is essential with consideration for central intravascular monitoring. Cardiac pacing should be considered for symptomatic bradydysrhythmias that are not responsive to treatment; however, the blood pressure may not respond despite the increase in heart rate. The use of cardiopulmonary bypass has been reported. Monitor ECG and vital signs for at least six hours after any alleged ingestion of immediate release preparations. Any symptomatic patients should be admitted for monitoring. All overdoses of sustained release products should be admitted and monitored for 24 hours.

Antidotes/ Specific Treatments**:**

1) **Atropine: Initial treatment for bradycardia. Dose 0.5-1 mg every 2-3 minutes for a total dose of 3 mg. May not be useful because of global myocardial depression, and not increased vagal tone.**
2) **Calcium**: Increases extracellular concentration gradient with increased movement via other calcium channels. Reverses decreased contractility, but may not reverse sinus node depression, AV nodal conduction, or peripheral vasodilation. One ampule of calcium chloride (10 mL of 10% $CaCl_2$) has three times as much calcium as calcium gluconate. One amp is slowly pushed over 3-5 minutes and may be repeated every 5-10 minutes. The effect is transient, and redosing or an intravenous drip may be necessary. **Adverse effects**: $CaCl_2$ causes sclerosis of vessels and should only be given via central

line and avoided in children. May cause lethal dysrhythmias in setting of digoxin toxicity, unless digoxin specific Fab fragments are given first.

3) **Catecholamines**: To stimulate cardiac beta-1 and peripheral alpha-1 adrenergic receptors. A direct-acting adrenergic agonist (i.e., norepinephrine or phenylephrine) is preferred.
4) **Glucagon**: Activates adenylcyclase via a G-protein receptor bypassing beta receptors. Primarily for beta-adrenergic blocker intoxication, but should be considered for severe cardiac depression. Dose is 2-5 mg slow IV push and can be repeated in 5-10 minutes for a total of 10 mg. Pediatric loading dose is 50-150 micrograms/kg. If effective this bolus should be followed by a continuous infusion at a rate of the dose the patient responded to per hour. **Adverse effects**: Vomiting and glucose intolerance.
5) **Hyperinsulinemia/Euglycemia***: This is the mainstay of therapy. Call for this early so that it can be mixed. In the meantime, you can use the above agents to mitigate hypotension and decreased inotropy. Correction of CCB-induced hyperglycemia, improved carbohydrate metabolism in cardiac myocytes, and positive inotropy are suggested mechanisms for action of high dose insulin while maintaining normal blood glucose levels. Bolus 1 U/kg with 1 amp of D50, followed by 1 U/kg/h and glucose infusion to maintain serum glucose levels between 100-200 mg/dL. Serum potassium, magnesium, and phosphate should be monitored and replaced as needed. Initially blood glucose should be checked every 15 minutes until stable, then every 30 minutes for first couple of hours.

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