Calcium Channel Blocker and Beta Blocker Overdose
“A Dab Will Do Ya”

No disclosures to report

Objectives
- Introduction
- Pathophysiology and Pharmacokinetics
- Toxic Effects
- Review of Toxin Induced Cardiovascular Failure
- Differential and Work-Up
- Therapy Options
- “Newer” and More Controversial Therapies
- Conclusion
- References
Increasing prevalence of cardiovascular disease
Increasing use of cardiovascular medications
Annual Report of the American Association of Poison Control Centers
- 102,766 CV Medication Exposures
- CCBs most often implicated
Identifying and treating patients with toxic effects is complex
ABC's and Resuscitative Protocols
"Interesting" Therapies

Introduction
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Affinity to L-type Calcium Channels

- Dihydropyridines: Vascular smooth muscle
- Phenylalkylamines: Vascular and Cardiac
- In an OD situation receptor selectivity is lost

Blocking of L-type Calcium Channels

- Interferes with release of Ca from sarcoplasmic reticulum
- Interferes with formation of actin-myosin complex
- Decreases inotropy and chronotropy
- Smooth muscle relaxation

Calcium Channel Blockers
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Well absorbed in gastrointestinal tract

- Metabolized via cytochrome system
- Risk of drug/drug interactions
- Highly protein bound
- Large volume of distribution
- HD is not useful in OD situation

Calcium Channel Blockers
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Calcium Channel Blockers

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- Developed in the 1960’s
- Hypertension, CHF, thyrotoxicosis, angina, ACS, and essential tremor

- Two Beta Receptors of Importance
  - Beta-1: Cardiac myocytes
  - Beta-2: Lungs and vascular smooth muscle

Beta Blockers
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- Beta-1
  - G coupled, cyclic-AMP receptors
  - Calcium release from sarcoplasmic reticulum
  - Increases inotropy and chronotropy

- Beta-2
  - Smooth muscle relaxation
  - Selective or non-selective
    - Non-selective: Propranolol
    - Selective: Metoprolol

- Lipophilicity (Propranolol)
  - Increased CNS penetrance
  - Increased risk of seizures (Therapeutic dosing)
  - Decreased level of consciousness (Overdose)

- Membrane stabilizing activity (Propranolol or Acebutolol)
  - Sodium channel blockade / Cardiac fast channels
  - QRS widening
  - Increased risk of dysrhythmia
  - Seizure activity and diminished consciousness

Beta Blockers
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**The Toxic Effects**

- Calcium Channel Blockers
  - Inhibition of Calcium influx through L-type channels
  - Inhibition of myocardial fast sodium channels
  - Inhibition of insulin release from pancreatic islet cells
    - Hypoinsulinemia and Hyperglycemia
  - Inhibition of glucose uptake in peripheral tissues

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**The Toxic Effects**

- Calcium channel blockade triggers the heart to change metabolism
  - Carbohydrate metabolism [Stressed State]
  - Free fatty acid oxidation [Non-Stressed State]

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**The Toxic Effects**

- Profound vasodilation!!!
- Decreased systemic vascular resistance!!!
- Bradycardia!!!
- Conduction delays!!!
- Lactate accumulation!!!
- Metabolic acidosis!!!
- Altered mental status!!!
- Seizures!!!
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- Short list with Bradycardia and Hypotension
- Acute Coronary Syndrome ( Inferior MI with various blocks)
- Hyperkalemia
- Endocrine Disorders (Hypothyroid)
- Poisoning
  - Opiates
  - Cholinergic toxicity

**Differential Diagnosis**

- Short list with Bradycardia and Hypotension
- Acute Coronary Syndrome ( Inferior MI with various blocks)
- Hyperkalemia
- Endocrine Disorders (Hypothyroid)
- Poisoning
  - Opiates
  - Cholinergic toxicity

**Clinical Work-Up**

- ABC’s
- IV Access
- EKG
- Review medications!! (Regular vs Sustained Release)
- Laboratory studies (Blood / Urine)
- CT Head with altered mental status
- Consider the Blood Sugar Level
- Identify the “type” of shock if unstable

**Clinical Work-Up**

- Variability of presentation depending on ingestion
- Verapamil and Diltiazem -> Bradycardia and Heart Blocks
- Nifedipine -> Hypotension + Reflex tachycardia
- Beta Blockers -> 1st degree heart block with QRS interval prolongation
- High risk for ventricular dysrhythmia
Therapeutic Options

ABC’s!!!
TEAMWORK!!!
Consultation with Toxicologist / Poison Control Center
– Improved mortality

Initial Treatment
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- Prevention of absorption (Seems like a good idea)
- Caution
- Do not induce emesis
- Activated charcoal
  - Non-sustained product
  - 1-2 hours post ingestion
  - 50% reduction at 2 hours from ingestion
  - 25 - 100 grams + Sorbitol

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- Whole bowel irrigation
  - Sustained release medication
  - Hemodynamically stable
  - Polyethylene glycol 1500 – 2000 mL/h (until clear)
  - Beware:
    - Prone to rapid decompensation
    - Non-intubated aspiration risk

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- High dose insulin therapy, an evidence based approach to beta blocker/calium channel blocker toxicity

  - Insulin-Glucose as Adjunctive Therapy for Severe Calcium Channel Antagonist Poisoning
  - High-dose insulin therapy in beta-blocker and calcium channel-blocker poisoning
Insulin and Glucose

**Historical perspective**

- Experimentation on treating verapamil poisoned canines
- Over 20 years ago
- Circulatory shock, acidosis, and mild hyperglycemia responded well with epinephrine and glucagon

**CCB**

- Insulin infusion with slow and steady hemodynamic improvement
  - Sustained contractility and organ perfusion
  - Protection from increased doses of CCB

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**Clinical Tox 2011; 49: 277-283**
**Emerg Med Clin N Am 2014; 32: 79-102**
**Clin Tox 2014; 52: 926-944**
**EB Medicine 2014; 16(2)**

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**Insulin and Glucose**

- High-dose insulin euglycemic therapy has become the mainstay
- First line intervention
- Insulin supports the heart metabolically during shock states
- Metabolism changes from free fatty acids to glucose in stress states
- Insulin promotes carbohydrate metabolism
  - Increases glucose uptake by myocytes
  - Increases lactate uptake providing secondary energy substrate
- 0.5 – 1U/kg of regular insulin, followed by infusion of 1U/kg/hr
- Consider ideal body weight

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**Insulin and Glucose**

- Insulin is titrated to achieve MAP goal
- Concurrent glucose administration followed by infusion
  - 25g Dextrose with initial insulin bolus
  - 0.5g/kg/hr infusion
  - Consider increased glucose concentration infusion
- Frequent glucose monitoring

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**Slide 45**

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  - Consider increased glucose concentration infusion
- Frequent glucose monitoring
Seems like a natural reversal agent
- Evidence is weak
- Dosage not well defined / no dose-effect relationship
- 10–20mL of 10% CaCl$_2$ or 30–60mL 10% Calcium gluconate
  - Which provides more calcium?
  - Which is delivered in a single dose?
  - Calcium gluconate via peripheral syringe present in Accudose
  - CaCl$_2$ usually delivered in IVPB

Single dose?
- Efficacy not well defined
- Too much Ca$^{2+}$ can be harmful

Calcium Clinical Tox 2011; 49: 277-283
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Commonly used, variable success
- Not necessarily failure of treatment, too profound of toxicity
- Standard dosing may not be adequate
- Push the limits

Vasopressors and Inotropes
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**Glucagon**
- Studied since the 1960's
  - Increased chronotropic and inotropic effects
- Produced by the pancreas, glucose homeostasis
- Increases cAMP
- Decreased in CCB / BB OD
- Negative inotropic and chronotropic effects
- Bypasses normal catecholamine driven production of cAMP
- Early use may provide benefit
  - 3–5mg over 1-2 min, repeat 4–10mg, maint 2–5mg/h
  - Nausea / Vomiting

*References:*
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**Atropine**
- Used for the bradycardic and hypotensive patient
- Rarely effective in CCB or BB OD
- Studies provide limited evidence
  - 0.5–1mg every 2 minutes, up to 3mg may be trialed

*References:*
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**Sodium Bicarbonate**
- Widened QRS
  - Indicative of sodium channel blockade
  - If the QRS shortens, consider infusion
  - Not routinely used for treatment of CCB / BB OD
Phosphodiesterase Inhibitors
- Amrinone, Enoximone, Milrinone
- Prevent degradation of cAMP
- Possible efficacy with concomitant use with Glucagon
- Side effect: Hypotension
- May antagonize the effects of nitroglycerin
- Long half-life

Transvenous or Transthoracic
- Consideration for patient refractory to other therapies
- Goal HR ~ 50 – 60 bpm
- Efficacy is uncertain
- While HR rises, inotropy does not necessarily rise

Extracorporeal Membrane Oxygenation
- Itra-Aortic Balloon Pump
- No clear guidelines
- ARDS Studies
- Few reports of good outcomes
- Refractory to all other therapies
Both CCBs and BBs are highly protein bound
- Large volume of distribution
- Hemodialysis is not indicated and is not useful
  Unless...
  - Atenolol, Acebutolol, Nadolol, or Sotalol
  - Unique hydrophilic properties
  - Minimal protein binding

Hemodialysis
Clinical Tox 2011; 49: 277-283
Clin Tox 2014; 52: 926-944
EB Medicine 2014; 16(2)
Lipid Emulsion Therapy

- Use has increased dramatically in the management of CV instability in overdose of cardiotoxic medications
- Initially described for treatment of cardiovascular collapse related to local anesthetic toxicity
- Exact mechanism of action is not completely known
- Enhances fatty acid transport across the mitochondrial membrane improving cellular energy
- Increasing cardiac myocyte calcium levels -> increased inotropy
- New medium allowing for lipid soluble drug equilibration (pulling toxin from the tissue)

20% Lipid Emulsion
- 1.5mL/kg bolus over 2 – 3min, followed by a 0.25mL/kg/min infusion
- A repeat bolus may be given for asystole or PEA
- Will interfere with certain laboratory testing
- Consider following Triglycerides

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- Consider following Triglycerides
L-Carnitine

Refractory shock despite maximal therapy

6g L-Carnitine IV, followed by 1g every 4 hours

Theory

- Reversal of free fatty acid metabolism from glucose in the myocytes
- Decreasing insulin resistance
- Increasing uptake and oxidation of free fatty acids
Methylene Blue

1. Accumulation of cGMP in vascular smooth muscle results in vasodilation and decreased response to vasopressors
2. Production of cGMP decreased through inhibition of nitric oxide synthase and guanylate cyclase

- 2 mg/kg over 20 min, followed by 1 mg/kg/hr infusion

All good things must come to an end!

Conclusion
Conclusion

1. Do not allow yourself to be lulled into complacency
2. Do the puzzle pieces fit together?
3. Critical thinking is REQUIRED
4. Not a time to be cavalier, to colleagues and families
5. TEAMWORK!!!  COMMUNICATION!!!  DEDICATION TO THE
DETAILS!!!

References


Holger Kaczmarek, Jow rien Eiger, and Pierre Dargan. Digoxin Toxicity. EB Medicine; 16(2).


Calcium Channel Blocker Overdose - Amlodipine
Case Study #1

Background
- 45 year old male - unemployed, divorced, 1 estranged son
- Medical/Surgical History: HTN, Pancreatitis, Testicular Cancer s/p Orchiectomy 1996, Kidney Stones s/p stent placement, Depression, Drug/Alcohol Abuse
- Psych/Social History: 5 previous suicide attempts

More background
- 8 previous ED visits over past 3 years
- 3 days prior to admission: First inpatient admission to hospital – Librium overdose
- Left AMA
ARRIVAL

- Found down by mother, brought to ED via EMS
- Initial GCS: 5
- Initial VS: 35.0° C axillary, HR 114, RR 5-6, 99% on NRB, 115/70
- Required immediate intubation in ED

Initial ED Assessment

- GEN: GCS 5, responsive to noxious stimuli only
- HEENT: Pupils constricted but equal
- HEART: Tachy regular, no S3, S4, or murmurs
- LUNGS: Distant, otherwise R/L:
- ABD: S/ND,
- EXT: Upper extremity tattoos present, warm, acyanotic, cap refill < 3
- NEURO: Unable to fully assess

Labs on arrival

- Na: 143
- K: 3.4
- Ca: 3.6
- BUN: 8
- Creatinine: 1.00
- Mg: 1.3
- Phos: 3.5
- Lactate: 3.5
- Positive for alcohol/benzodiazepines

ABG (post intubation):
- pH: 7.42/pCO2 42/pO2 189/Bicarb 27/Base Excess 2.0
ED Course (~3 hours)
- Intubated upon arrival
- HR 110s/Normotensive
- Within 1 hour of arrival, profoundly hypotensive (60s-70s/40s) with HR 80s
- Overdose medications determined by pharmacy: Seroquel, Hydroxyzine, and Amlodipine
- Sedation switched from Propofol/Fentanyl to Versed/Fentanyl and eventually stopped

ED course continued
- EKG: No evidence of dysrhythmias or QT prolongation
- Given 3L NS bolus
- Norepinephrine initiated
- Calcium Gluconate
- Magnesium Sulfate
- Immediate transfer to MICU

MICU Arrival @ ~2230
- Central Access obtained – R TL IJ
- Right radial arterial line placed
- Norepinephrine drip increased to maximum dose
- Vasopressin, Epinephrine, Phenylephrine and Dopamine drips initiated to maintain MAP>60mmHg
- Initial Insulin bolus of 83 units given (1 unit/kg)
- ~0000: Insulin drip initiated at 35 units/hr, subsequent increases to 45 units/hr, 68 units/hr, 88 units/hr, 110 units/hr, 130 units/hr to eventual rate of 166 units/hr Q15 minute FSBS
- Several amps D50 administered
- Continuous D10 infusion
MICU Arrival continued...

- 5mg Glucagon given IVP, followed by infusion at 5mg/hr
- Methylene Blue: 2mg/kg for 20 min, followed by 1mg/kg continuous infusion
- 1L NS Bolus given with NS infusion at 200mL/hr
- Banana Bag at 150mL/hr
- 1L LR Bolus followed by LR at 150mL/hr
- 0.45% Sodium Chloride + 100mEq Sodium Bicarbonate at 125mL/hr
- Hydrocortisone
- Cefipime, Vancomycin, Levaquin
- Q1 hour labs
- Q10-15 minutes FSBS

Why did we administer these medications?
- High dose insulin: positive inotropic effects; increased intracellular glucose transport;
- Glucagon: increases heart rate and myocardial contractility, and improves atrioventricular conduction;
- Methylene Blue: has several actions that may counteract the effect of increased nitric oxide synthase stimulation.

Electrolyte replacement
- 140 mEq KCl IV given over 7 hours; 80 mEq KCl given via OGT
- 1g Calcium Gluconate
- 1g Calcium Chloride
- 3g Magnesium Sulfate
- 16mmol Potassium Phosphate
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What exactly is going on?

- Severe metabolic acidosis
- Distributive shock
- Anuric Renal Failure
- Pulmonary edema secondary to shock resuscitation
- Thrombocytopenia
- Multiple electrolyte abnormalities
- Possible septic shock with developing leukocytosis

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The next 12 hours...

- 1 unit PRBCs
- 4g magnesium sulfate, 70 mEq IV KCl, 30mmol Potassium Phosphate
- 2L LR Bolus
- 16 hours following admission: CRRT initiated – pt with PROFOUND hypotension (50s/20s)
- Insulin drip decreased to 41.5 units/hr

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Per MICU attending physician...

“The patient is profoundly ill. His physiology is secondary to a combination of issues including multiple mechanisms from his poly-ingestion and SIRS response with distributive shock. We will continue aggressive supportive care, but he has shown very little progress throughout the day despite great efforts. We will continue multiple vasopressors, aggressive ventilator measures, CRRT, electrolyte repletion, empiric antibiotics, blood product repletion and monitoring. Updated mother and other family multiple times throughout the day. Very poor prognosis.”
24 hours later...

- Opened eyes to voice, began following simple commands
- Net + 28L fluid!!
- Severe ARDS, paralyzed with Cisatracurium due to dyssynchrony with vent
- Only 2 pressors (Norepinephrine and Vasopressin)
- Elevated bladder pressures (highest 25)
- Shock Liver
- Insulin drip off, D50 q4hrs for hypoglycemia

Nursing care the first 24 hours...

- 4-5 RNs first several hours
- 12-16 IV pumps running with continuous medications
- MULTIPLE titrations/rate changes/IV bag changes
- Q1 hr labs
- Q15 minute – q1hr FSBS
- Ventilator management
- Paralytic administered/titrated with train of four assessment
- CRRT initiation/management
- General nursing care/assessment
- Other medications

Overall course

- 4 days later: Off all vasopressors
- 5th day: STAT urology consult due to significant penile/scrotal edema
- 8 days later: CRRT stopped
- 9th day: Extubated to nasal cannula (significant delirium/encephalopathy)
- 12 days later: Transferred to floor
- 16th day: Transferred to inpatient psychiatry
- 22 days later: Discharged home.
Case Study
CCB Overdose: Verapamil

Background
› 23 yo female presenting with CCB overdose
› AX: Nitro, Doxycycline, Tylenol, Biaxin, Citalopram, Etomidate, Geodon, Lamictal, Peanut.
› HX: depression, previous suicide attempts x4, anorexia nervosa, arthritis, multiple knee and shoulder surgeries, anemia, and sinus tachycardia.
› Prior to arrival pt hanging out with friend described by family as a bad influence.

Arrival
› Discovered that pt had convinced a physician to prescribe her Verapamil, which she filled earlier that day and proceeded to ingest entire bottle.
› Taken to ED by friend when she began losing consciousness.
› Pt started seizing in route and was actively seizing upon arrival. Pt intubated and given Ativan.
Labs on Arrival
- Lactate 14.4
- ABG - pH 6.74, CO2 48, PaO2 94, HCO3- 6.5
- Glucose 483
- Cr 1.92
- K 4.7
- Anion gap 29
- Ca initially high and quickly dropped

ED Adventure
- Pt in 3rd degree block with HR ~20 and SBP ~60.
- Given calcium, activated charcoal, Epi, bolus of LR, Atropine, 20% lipid emulsion therapy, and high dose insulin therapy.
- Pt bolused with 70 units of insulin and started on gtt at 70u/hr.
- Intravenous pacemaker placed after external pacing failed.

Some Rationale
Effects of CCB overdose:
- Hypotension from negative effects on inotropy, chronotropy, and peripheral vascular tone.
- Hyperglycemia from blocked release of insulin.

Effects of treatment:
- High dose insulin has inotropic effect.
- Fat emulsion creates lipid 'sink.'
Holy moly, now you’re my patient!

Sooo…does anyone know how to treat CCB overdose?…

anyone,…anyone…

Bueller?

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Arrival to Unit 65

Pt arrived to the MICU from cath lab around 1430.

Pt connected to intravenous pacemaker, although now tachycardic.

Insulin running at 280u/hr!

Lipids infusing.

Pt on Epi gtt. Tried to titrate off in cath lab, but were unsuccessful.

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Life in room 6502

Pt’s BP becoming more unstable.

In light of further BP instability pt was bolused 1L NS, given another small dose of lipolytic methylene blue 1% (1mg/kg), 5mg glucagon, and started on more pressors.

NURSING: Learned we needed to tell lab to spin off lipids before running results.

Another 50ml of bicarb given for acidosis.

Pt started on a D10 gtt once lipids infused.
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Overnight...

- Pt also now requiring large amounts of KCL replacement due to intracellular shifts. 200mEq over the next 24hrs
- Overnight pt was weaned off one pressor, but then had to be restarted once she began waking up and needed sedation. Went through 47 bags of insulin in 24hrs
- Pt went through 47 bags of insulin in 24hrs and another 250ml bags over the next 24hrs.

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The next day...

- Pt off all vasopressors.
- MANY electrolyte replacements
- D20 gtt started to maintain blood glucose > 100 with insulin therapy.
- Blood sugar checks q30mins.
- Insulin therapy titrated down by 10% q30mins as pt's BP tolerated.
- Pt still had a severe metabolic acidosis.
- Pt had a lactate >2 for 4 days.

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Her Admission

- Insulin gtt titrated off after 72hrs.
- Pt's K initially high after insulin stopped, but resolved on its own as AKI resolved.
- Pt extubated after 48hrs. Floor status in 96hrs, and d/c'd after a 6 day admission. Pt thought by psych to have a conversion disorder.