Drugs that Make You Go Slow

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Objectives:
• List common medications that cause bradycardia and hypotension in overdose
• Describe treatment of calcium channel and beta blocker overdoses
Disclosure

• Speaker has no conflict of interest

• This presentation discusses uses of medication still under investigation which have not yet been approved for clinical use
Objectives

- List common medications that cause bradycardia and hypotension in overdose
- Know treatment of these overdoses
- Describe controversies in treatment
The Culprits

- Beta Blockers
- Calcium Channel Blockers
Incidence

• Cardiovascular Drugs
  – 3.74% of exposures reported to PCC in 2011
  – 11% of reported fatalities

• Highest mortality
  – Calcium channel blockers
Mechanism of Action

Mechanism of Action

# Beta Blockers

<table>
<thead>
<tr>
<th>Agent</th>
<th>Adrenergic Receptor Blocking Activity</th>
<th>Lipid Solubility</th>
<th>Sodium Channel Blocking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acebutolol</td>
<td>β₁</td>
<td>Low</td>
<td>Yes</td>
</tr>
<tr>
<td>Atenolol</td>
<td>β₁</td>
<td>Low</td>
<td>No</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>β₁</td>
<td>Low</td>
<td>No</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>α₁,β₁,β₂</td>
<td>High</td>
<td>No</td>
</tr>
<tr>
<td>Esmolol</td>
<td>β₁</td>
<td>Low</td>
<td>No</td>
</tr>
<tr>
<td>Labetolol</td>
<td>α₁,β₁,β₂</td>
<td>Moderate</td>
<td>No</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>β₁</td>
<td>Moderate</td>
<td>No</td>
</tr>
<tr>
<td>Nadolol</td>
<td>β₁,β₂</td>
<td>Low</td>
<td>No</td>
</tr>
<tr>
<td>Propranolol</td>
<td>β₁, β₂</td>
<td>High</td>
<td>Yes</td>
</tr>
<tr>
<td>Sotalol</td>
<td>β₁,β₂</td>
<td>Low to moderate</td>
<td>No</td>
</tr>
</tbody>
</table>

Mechanism of Action

Calcium Channel Blockers

• Location
  – Myocardial cells
  – Smooth muscle cells
  – β- islet cells of pancreas

• Types
  – Dihydropyridines
  – Non-dihydropyridines
### Signs and Symptoms of Toxicity

<table>
<thead>
<tr>
<th></th>
<th>Beta Blocker</th>
<th>Calcium Channel Blocker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>CNS Depression</td>
<td>Lipid soluble beta blockers</td>
<td>2° to hypoxia</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>AV block</td>
<td>AV block</td>
</tr>
<tr>
<td></td>
<td>Prolong QRS (Na⁺ channel blocking beta blockers)</td>
<td>Conduction disturbances</td>
</tr>
<tr>
<td>Effect on Glucose</td>
<td>None</td>
<td>Hyperglycemia</td>
</tr>
<tr>
<td>Metabolic Acidosis</td>
<td>Yes</td>
<td>More pronounced</td>
</tr>
</tbody>
</table>

*Shepherd G. Treatment of poisoning caused by beta adrenergic and calcium-channel blockers. AJHP. 2006;63:1828-35.*
Range of Toxicity

<table>
<thead>
<tr>
<th>Agent</th>
<th>Maximum Therapeutic Range</th>
<th>Threshold Dose for Referral</th>
<th>Lowest Reported Toxic Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atenolol</td>
<td>100 mg</td>
<td>200 mg</td>
<td>500 mg</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>25 mg</td>
<td>50 mg</td>
<td>1050 mg</td>
</tr>
<tr>
<td>Labetolol</td>
<td>300 mg</td>
<td>400 mg</td>
<td>6000 mg</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>100 mg ( \text{IR-} ) 450 mg ( \text{ER-} ) 400 mg</td>
<td>7500 mg</td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td>320 mg</td>
<td>240 mg</td>
<td>800 mg</td>
</tr>
<tr>
<td>Sotalol</td>
<td>160 mg</td>
<td>160 mg</td>
<td>560 mg</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>10 mg ( \text{IR-} ) 120 mg ( \text{ER-} ) 120 mg</td>
<td>30 mg</td>
<td></td>
</tr>
<tr>
<td>Diltiazem</td>
<td>12 hr- 320 mg 24 hr- 480 mg</td>
<td>12 hr- 360 mg 24 hr- 540 mg</td>
<td>IR- 360 mg ( \text{IR-} ) 30 m ( \text{ER-} ) 60 mg 12 hr- 700 mg 24 hr- NC</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>IR- 30 m ( \text{ER-} ) 60 mg</td>
<td>IR- 40 mg ( \text{ER-} ) 60 mg</td>
<td>IR- 260 mg ( \text{ER-} ) 600 mg</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>IR- 30 mg ( \text{ER-} ) 90 mg</td>
<td>IR- 30 mg ( \text{ER-} ) 120 mg</td>
<td>IR- 50 mg ( \text{ER-} ) 200 mg</td>
</tr>
<tr>
<td>Verapamil</td>
<td>IR- 160 mg ( \text{ER-} ) 480 mg</td>
<td>IR- 120 mg ( \text{ER-} ) 480 mg</td>
<td>IR- 160 mg ( \text{ER-} ) 720 mg</td>
</tr>
</tbody>
</table>

Indicators of Toxicity

- Beta blockers with high lipid solubility
- Diltiazem or verapamil
- XR formulations
Treatment

• Atropine
• Glucagon
• Calcium
• Vasopressors
• High dose insulin and dextrose
• Lipid emulsion therapy
Atropine

- Indication: bradycardia
- Mechanism
  - Anticholinergic
  - Antagonist of ACh at muscarinic receptors
- Dose
  - Bolus: 1 mg IV
  - May repeat twice
- Controversy
  - May be ineffective in severe overdose
Glucagon

Glucagon

- Indication: bradycardia + hypotension
- Mechanism
  - Activates G coupled receptor
  - Independent of β receptor
- Dose
  - Bolus: 5 mg IV bolus, may repeat in 5 minutes
  - Maintenance infusion: 3-5 mg/hr IV
- Controversy
  - Limited evidence
  - Causes nausea and vomiting
  - May deplete hospital supply

Calcium

Calcium

• Indication: hypotension
• Mechanism
  – Binds to calcium channels
  – Reverses the depression of cardiac contractility
• Dose
  – Bolus: 3000 mg (30 mL) calcium gluconate IV
  – May repeat boluses q10-20 minutes up to 3 doses
• Controversy
  – May need high doses in large overdoses

Vasopressors

- Indication
  - Hypotension

- Mechanism
  - Alpha and beta stimulation

- Dose (titrate to effect)
  - Norepinephrine: 0.05 mcg/kg/min
  - Epinephrine: 0.05 mcg/kg/min
  - Dopamine: 5 mcg/kg/min

High Dose Insulin

• Indication: cardiogenic shock
• Mechanism
  – Promotes carbohydrate metabolism
  – Increased inotropy that may be due to increased calcium influx
• Dose
  – Insulin
    • Bolus: 0.5-1 units/kg IV
    • Infusion: 0.5-1 unit/kt/hr (~35-100 units/hr)
  – Dextrose
    • Bolus: 25 grams IV
    • Maintenance infusion: 100-200 ml/hr to maintain euglycemia

High Dose Insulin

- Monitoring parameters
  - Glucose
  - Potassium

- Nursing considerations
  - High insulin drip rates
  - High utilization

- Controversy
  - Early treatment vs late “last ditch” treatment

Lipids Emulsion Therapy

• Indication: refractory hypotention with lipid soluble drugs

• Mechanism
  – Enhancement of fatty acid transport and increased energy
  – Increase cardiac calcium levels and increased inotropy
  – “Lipid sink” theory

• Dose (20% lipid emulsion)
  – Bolus: 1.5 ml/kg IV bolus
    • May repeat 1-2 times for asystole
  – Infusion: 0.25-0.5 ml/kg/min x 30-60 minutes
    • May increase if BP declines
Lipids Emulsion Therapy

• Side effects
  – Elevated lipase
  – Pancreatitis
  – Lung injury from fat emboli
  – Interference with lab values

• Controversy
  – More established for local anesthetic toxicity
  – Limited evidence
Methylene blue reverses recalcitrant shock in β-blocker and calcium channel blocker overdose

Nidhi Aggarwal, Yizhak Kupfer, Chanaka Seneviratne, Sidney Tessler

Aggarwal N, et al. BMJ Case Reports 2013. doi:10.1136/bcr-2012-007402
Take Home Points

• Dangerous medications
• Treatment controversies exist
• High-quality evidence is lacking
• Call Poison Control Center early
• Involve pharmacists
• Know where to find resources
Additional References

- Nickson C, Little M. Early use of high-dose insulin euglycaemic therapy for verapamil toxicity. MJA;191:350-2.
- Utah Poison Control Center personal communication and internal treatment documents.