High Dose Insulin Therapy: 
*Is it right for your patient?* 

Kristin Engebretsen, PharmD, DABAT 
Regions Hospital 
Kengebretsen@gmail.com 

Objectives 

- List 3 mechanisms of action of High Dose Insulin (HDI) in Toxin Induced Cardiogenic Shock (TICS) 

- Be able to compare and contrast 3 case scenarios where HDI may or may not be of benefit in TICS. 

HDI Mechanism 

- Increased inotropy 
- Increased intracellular glucose transport 
- Vascular dilatation.
Inotropy

- **Positive inotropy via generation of cAMP**
  - Insulin promotes glucose utilization and reduces gluconeogenesis.
  - At low doses, insulin causes sympathetic stimulation and positive inotropic effects.
  - At high doses, insulin exerts a combination of positive inotropy and peripheral vasodilation.

- **HDI's mechanism is not via adrenergic receptors in the manner of glucagon, but rather by generation of cAMP.**

### Increased Myocardial Glucose

- In the stressed state, the myocardium transitions from free-fatty acid oxidation such as lactate as a source of energy to carbohydrates.
- In overdose, the myocardial cells ability to utilize glucose is impaired, reducing optimal cardiac function.
- Insulin stimulates glucose metabolism, the cells preferred source of energy, and inhibits free fatty acid metabolism.
- Epinephrine and other adrenergic agents, which contribute to oxygen wasting and increase turnover of FFA.
Vasodilation

- Insulin is a vasodilator of the systemic, coronary, and pulmonary vasculature.
- Vasodilatory effects are due to enhancement of endothelial nitric oxide synthase (eNOS) activity by its effects on PI3K.
- Microvascular dysfunction is a hallmark of cardiogenic shock.
  - Insulin enhances microvascular perfusion at the capillary and pre-capillary level.

Enhancement of calcium signaling pathways

Insulin enhances Ca-ATPase activity of the SER which in turn improves contractility by enhancing excitation coupling.
Comparison of 3 cases

- **HPI:**
  - 49yo M, BBA with Hx of multiple medication suicidal ingestion

- **PMH:**
  - CAD s/p CABG and cardiac arrest.
  - Back pain
  - Depression

- **Meds:**
  - Tiasnidine - Metoprolol
  - Simvastatin - Benadryl
  - Mirtazapine - Seroquel
  - Topamax - ASA
  - Buproprion - Lisinopril

Physical Exam

- **VS:** T 99; HR 69, RR 12, BP 94/47, O2Sat 100% on O2

  - HEENT: NC/AT, PERRL 3mm. Oropharynx with some dried vomitus on the right lateral face
  - Lungs: Symmetric/Course BS bilaterally.
  - Heart: RRR/ no M/R/G.
  - Abdomen S/ND.
  - Extremities warm and well-perfused. Radial/Dorsalis pedis pulses 2+ and symmetric.
  - Neurologic: GCS 3, no clonus /rigidity

ED Course

- Pt Intubated
- Central line placed
- Head CT obtained/negative
- ECG obtained
- No Gastric Decontamination done
ECG - 2117 hrs

Final Note - Case 1

- Pt had episodes of bradycardia and hypotension
- HDI stopped, atropine given and EPI started.
- Pt received HDI, fluids, Na Bicarb, NE, CaCl, Mg, EPI
- Pt arrested, CPR started, Defibrilated. ROSC obtained. Family notified. Family requested DNR.
- 2nd episode of bradycardia and hypotension with one dose of epi and atropine given without effect.
- TOD: 03:35
Case 2

- 60 y.o. Male, BIBA after multiple drug ingestion
  - States he wanted to make up for missing this weeks BP meds
  - States he took 7 verapamil and 7 lisinopril tablets 3 hours prior
  - Missing 15 tablets of Verapamil, 2 lisinopril

- Blood Alcohol Level= 0.24

PMH:
  - Back Surgery
  - HNT
  - Rib Fracture
  - Depression

Medications
  - Verapamil ER 180mg
  - Lisinopril 5 mg
  - Triamterene-HCTZ 75-50 mg

Physical Exam

- VS
  - 1546-80/55, 97.9 F, HR 60, RR24, 95% RA
  - 1600-62/42, 98 F, HR 57, RR18, 95% RA

- HENT: PERRL, MM moist
- CV: RR, No M/R/G noted
- ABD: S/NT/ND
- Neuro: AxOx3, GCS 14

ED/Early ICU

- ECG obtained- showed sinus bradycardia
- Patient readily states he wants all cares given to save his life.
- Central line placed
- BP decreases to 62 systolic
- 2 Liters of Fluid given
- Patient intubated, OG tube placed/AC given
- HES insulin started with bolus 1u/kg and infusion started at 1u/kg/hr and titrated to 5u/kg/hr
  - CO ranged 9-10 area
Medications

- Dobutamine started (Art BP 55/15 @1900)
- Atropine (Pulse 40 @ 1930)
  - 1 mg boluses (3 mg given)
  - HR 99-98 but dropped quickly again
- Pacemaker placement (@2000)
  - Intra aortic balloon pump pacing
  - PA cath to measure heart pressures
  - (10/24 2300) CO ranging 6-12 and PCWP 10-12
- Calcium Gluconate
  - 1 gram Ca Gluc given and insulin increased to 6 u/kg/hr
  - BP rise to 90-92
  - CO still in supratherapeutic range
- Levophed started (@2255)
  - BP stopped declining, still low but stable
  - SVR remained low

Medications Continued...

- Phenytoin
  - SBP 82-85
- Vasopressin
  - After 45 minutes still no change in BP

Day # 2 (10/25 @ 0700)

- Patient sedated on propofol
  - Upon sedation patient awake and follows commands. Does not nod yes or no.
  - Stopped propofol in hopes of increasing BP
- UOP- adequate
  - Within last 8 hours ~ 2,036 ml
- SBP- still low but 90-92
- CO/CI 9.4/4.7
- Family- wife wants DNR/DNI
- Per nurse-BP responds well to calcium gluconate.
Change of Shift

• New practitioner on at 1500– chooses to taper off pressors and insulin at the same time against recommendations

• Previous practitioner does not follow wife’s wish for DNR/DNI b/c patient directly told him he wanted all cares given.

• Calcium Chloride IV started 5000mg/50 ml running at 5 ml/hr

• Tried to wean pacer and underlying rhythm was 45 bpm which was tolerated. Placed back on pacer at 70 bpm.

• UOP has been <30 ml/hr for last 2 hours (2300)

Day # 3 (10/26)

• ~0200-Downhill, CO/CI 6.8/3.4
  ▫ ABP 82 systolic
  ▫ UO low despite Lasix
  ▫ Fluid bolus given – no response
  ▫ Daughter updated by phone and wants full code
  ▫ Increase insulin, CaCl restarted, Levophed increased

• ~0500
  ▫ Per nurse- Notified MD of need to titrate up insulin/wean pressors

• ~0615
  ▫ Pt awake and restless due to decreased propofol for decreased BP.
  ▫ Ask patient if air hungry→ nods yes, Trying to talk around ETT tube

• ~1500, CO/CI 3/1.5
  ▫ No code blues is signed
  ▫ Hemodialysis- BP increased after dialysis
  ▫ Propofol off again
  ▫ Agitated patient and moves to command, does not nod yes or no.

Day # 4 (10/27)

• ~0400
  ▫ HR mid 60’s
  ▫ Levophed tapered throughout night to 8 mcg/kg/min.
  ▫ Insulin restarted but still remains low.

• ~0600
  ▫ CO/CI 7.6/3.0
  ▫ Dobutamine taper started.
  ▫ Follows commands, opens eyes to name, does not nod yes or no.
  ▫ Art BP 90/30
  ▫ UOP 30-35 ml/hr
Final Note

- 10/27 @ 0912: Family decided to end all supportive cares.
- Time of Death 1048.

Case 3:

- 30 yo F BIBA for RLQ abdominal pain.
- PMH:
  - Hypertrophic cardiomyopathy (HCM)
  - EF of 55%
  - Previous implanted cardioverter defibrilator

Physical Exam

- VS: 86/46, HR 73 (paced)
- Repeated physical Exam was normal and didn't explain abdominal pain
- Evaluated over next 3 hrs for abdominal pain.
  - Serum, urine tests, ultrasound, repeated physical exams, and CT.
- ECG paced rhythm with no changes compared to previous ECG.
ED Course

- Vital signs worsened 64/41, HR 70 (paced) despite 2L NS
- Patient became confused and admitted to taking all of her diltiazem, metoprolol and amiodarone 6 hours prior
- Another 2L NS
- 6 amps calcium gluconate (27mEq)
- HDI 0.5u/kg bolus, HDI infusion escalated to 10u/kg/hr.

Course/Treatment:

- CVP was 20mm Hg
- Echo showed worsening cardiac function (decreased EF and hypokinetic)
- 85min tx with fluids, calcium, and HDI therapy were ineffective
- Intralipid (20%) administered as 100ml bolus, followed by infusion of 1.5L over 1 hr.
- Within 15min of lipid bolus, BP was 110/60, and EF returned to baseline (55%)

Final Note: Case 3

- Diltiazem 1.44mg/kg (150-200), metoprolol 588mg/kg (50-300), amiodarone 2.7 mg/L (0.5-2)
- Patient admitted to ICU and had a stable hospital course and transferred to psych.
- Patient overdosed on the exact same medications 1 month later and presented to a different hospital.
- Discussed use of Intralipid and recommended against HDI.
- Recommendations not followed as aggressively as recommended
- Patient expired.
- Autopsy showed Diltiazem level 3x that of previous overdose.
Selection of Therapies for Toxin Induced Cardiovascular Shock
- Fluids-
- Atropine-
- Calcium
- Pressors
- HDI
- Lipid
- Balloon Bump/LVAD/Pacing/Extracorporeal methods.

Case Comparison
- All cases involved intentional overdoses of BB, CCB or Both
- All cases involved toxin induced cardiovascular shock.
- All hypotensive, 2 bradycardic, one paced
- 2 with significant underlying heart disease
Case 1: Review

- Case 1: 49 yo M Mulitple drug ingestion of Seroquel, Metoprolol and benadryl

- PMH: CAD, CAGB/Cardiac arrest

Case 1: A Closer Look

<table>
<thead>
<tr>
<th>Time</th>
<th>1900</th>
<th>2000</th>
<th>2100</th>
<th>2200</th>
<th>0000</th>
<th>2100</th>
<th>2130</th>
<th>0146</th>
<th>0222</th>
<th>0245</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin (U/h)</td>
<td>120</td>
<td>120</td>
<td>100</td>
<td>100</td>
<td>80</td>
<td>80-100</td>
<td>100</td>
<td>100</td>
<td>100-150</td>
<td>150</td>
</tr>
<tr>
<td>SBP</td>
<td>87</td>
<td>114</td>
<td>110</td>
<td>92</td>
<td>77-80</td>
<td>84</td>
<td>80-140</td>
<td>77</td>
<td>114</td>
<td>114</td>
</tr>
<tr>
<td>DBP</td>
<td>40</td>
<td>46</td>
<td>55</td>
<td>47</td>
<td>28-51</td>
<td>78</td>
<td>75</td>
<td>34</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>NE (mcg/min)</td>
<td>2</td>
<td>3</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Vaso</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
</tr>
</tbody>
</table>

Case 1: Evaluation

- Classic case of TICS responsive to HDI

- PCP uncomfortable with HDI's vasodilatory properties, wants higher BP/HR instead of looking at clinical S/Sx

- No use of SVR/CO or PE parameters.

- Concern for underlying CAD/Cardiac Arrest and use of pressors

- Vasopressors started, HDI discontinued

- Patient cardiac arrested.
Case 2: Review

- 60 yo M
- No underlying cardiac disease
- I only took 7 verapamil to make up for this week missed meds (15 missing)

ED/Early ICU

- ECG obtained- showed sinus bradycardia
- Patient readily states he wants all cares given to save his life.
- Central line placed
- BP decreases to 62 systolic
- 2 Liters of Fluid given
- Patient Intubated, OG tube placed/AC given
- HDI insulin started with bolus 1u/kg and infusion started at 1u/kg/hr and titrated to 5u/kg/hr
  - CO ranged 9-10 area

Medications

- Dobutamine started (Art BP 55/15 @1900)
- Atropine (Pulse 40 @ 1930)
  - 1 mg boluses (3 mg given)
  - HR 59-58 but dropped quickly again
- Pacemaker placement (@2000)
  - Intra aortic balloon pump pacing
  - PA cath to measure heart pressures
  - (10/24 2300) CO ranging 6-12 and PCWP 10-12
- Calcium Gluconate
  - 1 gram Ca Gluc given and insulin increased to 6 u/kg/hr
- BP rise to 90-92
- CO still in supratherapeutic range
- Levophed started (@2255)
  - BP stopped declining, still low but stable
  - SVR remained low
Day #3 (10/26)
- Change of Shift, PCP DC'd insulin and weaned off pressors
- ~0200-Downhill, CO/Cl 6.8/3.4
  - ABP 82 systolic
  - Fluid bolus given-no response
  - Daughter updated by phone and wants full code
  - Restart/Increase insulin, CaCl restarted, Levophed increased
- ~0500
  - Per nurse- Notified MD of need to titrate up insulin/wean pressors
- ~0630
  - Pt awake and restless due to decreased propofol for decreased BP.
    - Ask patient if air hungry→ nods yes, Trying to talk around ETT tube
- ~0800, CO/Cl 3/1.5
  - No code blue is signed
  - Hemodialysis- BP increased after dialysis
  - Propofol off again
  - Agitated patient and moves to command, does not nod yes or no.

Day #4 (10/27)
- ~0100
  - HR mid 60’s
  - Levophed tapered throughout night to 8 mcg/kg/min.
  - Insulin restarted
- ~0600
  - CO/Cl 7.9/3.9
  - Dobutamine taper started.
  - Follows commands, opens eyes to name, does not nod yes or no.
  - Art BP 96/56
  - UOP 30-35 ml/hr

Case 2: Evaluation
- TICS
- HDI therapy effective, but not enough
- Vasopressors added with additional info on SVR
- Vasopressors and HDI not enough to sustain pt
- IABP placed, Bypass considered
- Used CO/SVR, monitoring to guide therapy

Well managed case.
Case 3: Review

• 30 yo F
• I've got abdominal pain
• I lied, I took an overdose of Diltiazem/metoprolol/Amiodarone
• I will do it again.

Course/Treatment:

• CVP was 20mm HG
• 85min tx with fluids, calcium, and HDI therapy were ineffective
• Echo showed worsening cardiac function (decreased EF and hypokinetic)
• Intralipid (20%) administered as 100ml bolus, followed by infusion of 1.5L over 1 hr.
• Within 15min of lipid bolus, BP was 110/60, and EF returned to baseline (55%)

Case 3: Evaluation

• HDI titrated to 10u/kg/hr
• Echo showed no response/worsening with insulin
  ▫ PMH of HCM possibly making HDI ineffective
• Cardiogenic shock in presence of HCM treated with IV fluids and peripheral alpha agonists to increase SVR
  ▫ HCOM – fluids and vasopressors decrease left ventricular outflow obstruction
  ▫ Insulin’s potent inotropic activity and vasodilatory effect which could increase or actually induce outflow obstruction
Case 3: Evaluation

- Recommendations not taken
- Not treated as aggressively as recommended
- Focused on Insulin Therapy; When Insulin may have been contraindicated and Intralipid should have been given earlier
- Unknown even with our suggestions if this was a survivable ingestion.

Summary:

- No single antidote is the panacea
- Need monitoring capabilities such as SVR/CO/echo
- Need to monitor clinical presentation (MS, I/O, pulses), not just BP/HR when using HDI