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

Kristin Engebretsen, PharmD, DABAT
Regions Hospital
Kmengebretsen@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 to 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.
Insulin enhances Ca-ATPase activity of the SER which in turn improves contractility by enhancing excitation coupling.

Comparison of 3 cases

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

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

- **Meds:**
  - Tizanidine - Metoprolol
  - Simvastatin - Benadryl
  - Mirtazapine - Seroquel
  - Topamax - ASA
  - Bupropion - 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/Coarse 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
### Time Series

**Time**

<table>
<thead>
<tr>
<th></th>
<th>1900</th>
<th>2000</th>
<th>2100</th>
<th>2130</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>120</td>
<td>140</td>
<td>160-200</td>
<td>250</td>
<td>250</td>
</tr>
<tr>
<td>SBP</td>
<td>87</td>
<td>114</td>
<td>132</td>
<td>110</td>
<td>92</td>
<td>77-80</td>
<td>84</td>
<td>805</td>
<td>152</td>
<td>80</td>
<td>114</td>
</tr>
<tr>
<td>DBP</td>
<td>40</td>
<td>46</td>
<td>55</td>
<td>47</td>
<td>40</td>
<td>28-51</td>
<td>28</td>
<td>25</td>
<td>31</td>
<td>34</td>
<td>60</td>
</tr>
<tr>
<td>NE (mcg/min)</td>
<td>2</td>
<td>3</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaso</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D10 (ml/h)</td>
<td>200</td>
<td>200</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Time**

<table>
<thead>
<tr>
<th></th>
<th>0300</th>
<th>0311</th>
<th>0315</th>
<th>0330</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin (U/h)</td>
<td>250</td>
<td>250</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>67</td>
<td>52</td>
<td>134</td>
<td>61</td>
</tr>
<tr>
<td>DBP</td>
<td>22</td>
<td>21</td>
<td>26</td>
<td>18</td>
</tr>
</tbody>
</table>
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
  - Triamtrene-HCTZ 75-50 mg
Physical Exam

- VS
  - 1546-80/55, 97.9 F, HR 60, RR 24, 94% RA
  - 1600-62/42, 98 F, HR 57, RR 18, 95% RA

- HEENT: 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
- 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 39 → 48 but dropped quickly again

• Pacemaker placement (@2000)
  ▫ Intra aortic balloon pump pacing
  ▫ PA cath to measure heart pressures
    • (10/24 2300) CO ranging 8-12 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...

• Phenylephrine
  ▫ SBP 82-85

• Vasopressin
  ▫ After 45 minutes still no change in BP
Day # 2 (10/25 @ 0700)

- Patient sedated on propofol
  - Upon sedation vacation pnt 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 dose 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

- ~0613
  - 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 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 but still remains low.

- ~0600
  - CO/CI 7.9/3.9
  - Dobutamine taper started.
  - Follows commands, opens eyes to name, does not nod yes or no.
  - Art BP 96/36
  - 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 defibrillator
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 1.44ng/ml (130-190), metoprolol 388ng/ml (30-300), 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 Multple drug ingestion of Seroquel, Metoprolol and benadryl
- PMH: CAD, CABG/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>2130</th>
<th>2100</th>
<th>0000</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>120</td>
<td>140</td>
<td>160-200</td>
<td>250</td>
<td>250</td>
</tr>
<tr>
<td>SBP</td>
<td>87</td>
<td>114</td>
<td>132</td>
<td>110</td>
<td>92</td>
<td>77-80</td>
<td>84</td>
<td>80s</td>
<td>152</td>
<td>80</td>
<td>114</td>
</tr>
<tr>
<td>DBP</td>
<td>40</td>
<td>46</td>
<td>55</td>
<td>47</td>
<td>40</td>
<td>28-51</td>
<td>28</td>
<td>25</td>
<td>31</td>
<td>34</td>
<td>60</td>
</tr>
<tr>
<td>NE (mcg/min)</td>
<td>2</td>
<td>3</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VasoD10 (ml/h)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time</th>
<th>0300</th>
<th>0311</th>
<th>0315</th>
<th>0330</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin (U/h)</td>
<td>250</td>
<td>250</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>67</td>
<td>52</td>
<td>134</td>
<td>61</td>
</tr>
<tr>
<td>DBP</td>
<td>22</td>
<td>21</td>
<td>26</td>
<td>18</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 39→48 but dropped quickly again

- Pacemaker placement (@2000)
  - Intra aortic balloon pump pacing
  - PA cath to measure heart pressures

  - (10/24 2300) CO ranging 8-12 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/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
  - Restart/Increase insulin, CaCl restarted, Levophed increased

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

- ~0613
  - 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 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/CI 7.9/3.9
  ▫ Dobutamine taper started.
  ▫ Follows commands, opens eyes to name, does not nod yes or no.
  ▫ Art BP 96/36
  ▫ 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, UO, pulses), not just BP/HR when using HDI