The Hypotensive Poisoned Patient

Robert S. Hoffman, MD
Director, NYC PCC
Some Definitions

• Hypotension = Low blood pressure
  – Failure of macrocirculation

• Shock = Poor tissue perfusion
  – Failure of microcirculation
    • Macrocirculatory failure may be contributory
    • Attempts to improve macrocirculation often impair microcirculation

• The focus here is on toxin-related shock (microcirculation)
General Sense of the Audience

• A 32 year old man is brought to the hospital by ambulance following an attempted suicide
  – A suicide note was found along with an
  – Empty pill bottle (no label)

• Vital signs:
  – BP: 70/40 mm Hg
  – Pulse: 120/min
  – Respirations: 20/min with Sat 98% on room air
  – Afebrile
Question 1

• Your FIRST attempt to address the patient’s hypotension would be to give:
  – Intravenous fat emulsion (1.5 mL/kg of 20%)
  – Hypertonic sodium bicarbonate
  – Either dopamine, norepinephrine or epinephrine
  – A fluid bolus
  – High-dose insulin with glucose
When Fluids Might Not Be First

• An emergent antidote is indicated
  – Cyanide
  – Tricyclic with wide QRS complex
  – Respiratory failure (grave hypoventilation) from opioids
  – Etc

• Non-toxicologic
  – Severe right heart strain (pulmonary hypertension as in a massive pulmonary embolus
Case Continued

• That patient is given 2 Liters of IV crystalloid over about 20 minutes

• Repeat vital signs:
  – BP: 68/40 mm Hg (was 70/40 Hg)
  – Pulse: 115/min (was 120/min)
Question 2

Which of the following would you do?

- Another fluid bolus
- Insert central venous catheter and give more fluid only if the central venous pressure is low
- Ultrasound the inferior vena cave or jugular and give more fluid only if the central venous pressure is low
- Start epinephrine, norepinephrine or dopamine
- Intravenous fat emulsion (1.5 mL/kg of 20%)
Does Central Venous Pressure Predict Fluid Responsiveness?*: A Systematic Review of the Literature and the Tale of Seven Mares

Paul E. Marik, Michael Baram and Bobbak Vahid

*Chest 2008;134;172-178
DOI 10.1378/chest.07-2331
Conclusions

• This systematic review demonstrated:
  – A very poor relationship between CVP and blood volume
  – The inability of CVP to predict the hemodynamic response to a fluid challenge.

• “CVP should NOT be used to make clinical decisions regarding fluid management.”
Assessment of Circulatory Status

• Skin – Warm and well perfused vs. cold, mottled or vasoconstricted
• Urine output
• Mental status
• ECG – Impaired conduction often indicates impaired contraction
• Acid-base (lactate)
Utility of serum lactate to predict drug-overdose fatality

Case – Control design
50 cases: lactate 9.88
100 controls: lactate 2.76
AUC = 0.87
Cutoff of 3.0: 84% sens, 75% spec; OR 15.8
Toxicology is an Imperfect Science Art

• Good urine output occurs despite grave salt and water depletion
  – Glucose, salicylates, lithium
    • Obligate solute diuresis or impaired concentration (DI)
• Preserved mental status despite shock
  – Calcium channel blockers
• Misleading acid-base status
  – Direct metabolic acidosis toxins
Question 3

• An 18 year old with a history of depression presents 45 minutes after a witnessed ingestion of amitriptyline.

• In triage she is minimally responsive with:
  – BP 100/70 mm Hg, pulse 150/min

• Immediately on entering the ED the patient has a 30 second seizure
  – BP 70/40 mm Hg, pulse 100/min
Question 3

• The patient is intubated and ventilated
• A bolus of 0.9% NaCl is hung
• 3 boluses of hypertonic sodium bicarbonate (44.4 mEq each) are given
• A dose of activated charcoal is given via NG tube
• The ECG is improved but the BP is 80/60 mmHg
**Question 3**

• In a TCA overdose whose blood pressure is poor after fluids and bicarbonate, which of the following therapies would you give next
  – More fluid
  – More bicarbonate
  – Dopamine
  – Norepinephrine
  – Intravenous fat emulsion (1.5 mL/kg of 20%)
Beneficial Effect of Norepinephrine in the Treatment of Circulatory Shock Caused by Tricyclic Antidepressant Overdose


LUIS TEBA, MD, FRANKLIN SCHIEBEL, MD, HARAKH V. DEDHIA, MD, VALERIE A. LAZZELL, MD

FIGURE 1. Systemic systolic BP (SBP), cardiac index (CI), and systemic vascular resistance index (SVRI): admission values (t₀) and values during dopamine (t₁) and norepinephrine (t₂) infusions. □, case 1; ■, case 2.
Response to Dopamine vs Norepinephrine in Tricyclic Antidepressant-induced Hypotension

T. Paul Tran, MD, Edward A. Panacek, MD, Kenneth J. Rhee, MD, Garrett E. Foulke, MD

- Retrospective analysis
- 26 hypotensive TCA overdoses
- Response to dopamine or norepinephrine
  - Norepinephrine pts had lower initial BPs
Results

• Dopamine: 9/15 responded (60%)
• Norepinephrine: 11/11 responded (100%)
• All 6 patients who failed dopamine at doses as high as 50 ug/kg/min responded to norepinephrine

• Animal models have conflicting results
More on Dopamine

• Pressor effects dependent on presynaptic stores of norepinephrine
• Poor effect when stores are low
  – Antidepressants, disulfiram, etc
• Exaggerated effect when presynaptic stores high
  – MAO inhibition
Tyrosine \[ \downarrow \] Tyrosine-3-monoxygenase

DOPA \[ \downarrow \] L-aromatic amino acid decarboxylase

Dopamine \[ \downarrow \] Dopamine β-hydroxylase

NE

MAO

NE

NE

NE

NE

NE

NE

NE
“LIPID RESCUE” FOR TRICYCLIC ANTIDEPRESSANT CARDIOTOXICITY

J Emerg Med 2012 Epub

Michael Stephen Blaber, MBChB,* Jamal Nasir Khan, MRCP,† Judith Anne Brebner, MRCP,‡ and Rachel McColm, MRCP§

100 mL of 20% lipid-emulsion administered
Narrowing of ECG complexes seen, normalization of pH achieved, improvement of blood pressure (168/86), patient stabilised and transferred to ICU

Persistent broad complex tachycardia
Cardiac arrest: 11 min duration

pH after 100 mL 8.4% NaHCO₃
pH after 200 mL 8.4% NaHCO₃

pH after 250 mL 8.4% NaHCO₃ + 100 mL 20% lipid-emulsion

Sinus rhythm restored

pH
0 10 20 30 40 50 60 70 80 90 100 110
0 10 20 30 40 50 60 70 80 90 100 110

Time from arrival (min)
Tricyclic Antidepressant Overdose in a Toddler Treated With Intravenous Lipid Emulsion

David Hendron, Gareth Menagh, Euan A. Sandilands and Damian Scullion

Pediatrics 2011;128:e1628; originally published online November 7, 2011;
DOI: 10.1542/peds.2011-0867
Intralipid Outperforms Sodium Bicarbonate in a Rabbit Model of Clomipramine Toxicity


Martyn Harvey, BHB, MBChB, FACEM
Grant Cave, BHB, MBChB, FACEM

From the Department of Emergency Medicine, Waikato Hospital, Hamilton, New Zealand (Harvey); and the Department of Intensive Care Medicine, Monash Medical Centre, Melbourne, Australia (Cave).
No Antidotal Effect of Intravenous Lipid Emulsion in Experimental Amitriptyline Intoxication Despite Significant Entrapment of Amitriptyline

Erik Litonius¹, Tomohisa Niiya¹*, Pertti J. Neuvonen² and Per H. Rosenberg¹
Question 3

- In a TCA overdose whose blood pressure is poor after fluids and bicarbonate, which of the following therapies would you give next
  - More fluid
  - More bicarbonate
  - Dopamine
  - Norepinephrine
  - Intravenous fat emulsion (1.5 mL/kg of 20%)
Question 4

• A 23 year old woman arrives 8 hours after an intentional overdose of verapamil
• Vital signs: BP 80/50 mmHg; Pulse ~30/min
• Mental status: Alert and oriented
• Glucose: 20 mmol/L (360 mg/dL)
• ECG: next slide
Assessment of hyperglycemia after calcium channel blocker overdoses involving diltiazem or verapamil

Michael Levine, MD; Edward W. Boyer, MD, PhD; Charles N. Pozner, MD; Ann-Jeannette Geib, MD; Todd Thomsen, MD; Nathan Mick, MD; Stephen H. Thomas, MD

Composite end points of in-hospital mortality, the necessity for a temporary pacemaker, or the need for vasopressors

Crit Care Med 2007; 35:2071–2075
Question 4

• 4 liters of 0.9% NaCl and 9 grams of calcium gluconate are given without response, which of the following would you do next?
  – Address the heart rate (atropine or pacemaker)
  – Start a pressor (Epi, NorEpi, or dopamine)
  – IV Glucagon
  – High-dose insulin euglycemia therapy
  – Intravenous fat emulsion (1.5 mL/kg of 20%)
CLINICAL SIGNS OF TOXICITY

YES

↓

O₂, cardiac monitoring, IVs
(central line if possible), intubation PRN
↓

Decontamination if indicated
by (AC if ingestion < 1 h and
no contraindication. MDAC if
sustained-released or enteric-coated
preparations; WBI can be considered in
in those cases if no contraindication)
↓

Atropine for symptomatic bradycardia
IV fluids
↓

Vasopressors
Dopamine (first line treatment)

NO

↓

O₂, cardiac monitoring, IVs
↓

Decontamination if indicated
by (AC if ingestion < 1 h and
no contraindication. MDAC if
sustained-released or enteric-coated
preparations; WBI can be considered in
in those cases if no contraindication)
↓

Observation in ED or ICU

CCB ingestion

↓

Calcium Chloride 10% 10–20 ml
(0.2 ml/kg) or Calcium Gluconate 10%
30–60 ml (0.6 ml/kg) IV in 5 min
Repeat Q10–20 min PRN for 3–4 doses
Consider infusion

BB ingestion

↓

Glucagon 2–10 mg (50–150 μg/kg)
Repeat Q10 min PRN
Consider infusion
# Verapamil Poisoned Dogs

<table>
<thead>
<tr>
<th></th>
<th>Pulse</th>
<th>Cardiac Output</th>
<th>LV dP/dT</th>
<th>Mean Aortic BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxicity</td>
<td>49</td>
<td>1.6</td>
<td>981</td>
<td>36</td>
</tr>
<tr>
<td>Atropine</td>
<td>62*</td>
<td>2.5*</td>
<td>803</td>
<td>43*</td>
</tr>
</tbody>
</table>

CCB Poisoned Patients

• Multiple case reports of atropine failures
  – Publication bias
  – Selection bias

• Single prospective case series
  – Only 25% success rate
By 30 minutes, systolic blood pressure had decreased in the sham-treatment group ($P<0.01$ versus control group). Treatment with insulin or glucagon prevented further decreases in systolic blood pressure. Systolic blood pressure fluctuated during epinephrine treatment.
Hemodynamic Effects of Intravenous Fat Emulsion in an Animal Model of Severe Verapamil Toxicity Resuscitated with Atropine, Calcium, and Saline

Theodore C. Bania, MD, MS, Jason Chu, MD, Eric Perez, MD, Mark Su, MD, In-Hei Hahn, MD
Methods

• 14 dogs instrumented extensively
• Verapamil toxicity, defined as a 50% decrease in MAP
• All dogs got atropine and calcium chloride (15 mg/kg q 5min)
• Randomized
  – IFE (7 mg/kg of 20%) IV
  – Or equivalent volumes of 0.9% normal saline
Results 1

The graph illustrates the change in mean arterial pressure (in mm Hg) over time (in minutes) after the beginning of intravenous fat emulsion or saline infusion. The x-axis represents time (minutes) after the beginning of infusion, and the y-axis shows the mean arterial pressure.

- **Fat Emulsion** group shows a decrease in mean arterial pressure starting at 15 minutes, with a significant drop marked by an asterisk at 30 minutes.
- **Fat Emulsion with Verapamil** group also shows a decrease in mean arterial pressure starting at 15 minutes, with a significant drop marked by an asterisk at 30 minutes.
- **Control** group remains relatively stable with a slight decrease in mean arterial pressure over time.

Verapamil was administered at a rate of 2 mg/kg/min, as indicated by the arrow on the x-axis.
Results 2

- Fat Emulsion
- Fat Emulsion or Saline
- Control

Percent Survival

Time (minutes) after beginning of Intravenous Fat Emulsion or Saline Infusion

Verapamil at 2 mg/kg/min
Question 4

- 4 liters of 0.9% NaCl and 9 grams of calcium gluconate are given without response, which of the following would you do next?
  - Address the heart rate (atropine or pacemaker)
  - Start a pressor (Epi, NorEpi, or dopamine)
  - IV Glucagon
  - High-dose insulin euglycemia therapy
  - Intravenous fat emulsion (1.5 mL/kg of 20%)
Question 5

• In addition to improved inotropy which of the following is a known benefit of high-dose insulin therapy
  – Improved chronotropy
  – Tight glucose control
  – Decreased systemic vascular resistance
  – Decreased myocardial oxygen consumption
Muniyappa R: Endocrine Reviews 28: 463–491, 2007)
Muniyappa R: Endocrine Reviews 28: 463–491, 2007)
In addition to improved inotropy which of the following is a known benefit of high-dose insulin therapy

- Improved chronotropy
- Tight glucose control
- Decreased systemic vascular resistance
- Decreased myocardial oxygen consumption
Other Options

- Phosphodiesterase inhibitors
- Some form of extracorporeal life support
  - Aortic balloon pumps
  - Extracorporeal membrane oxygenator
  - Bypass
  - Etc.
- Newer consideration
ECLS

- Small
- Portable (76 lbs)
- Supports cardiac output without oxygenation
- Inexpensive $4500
Sixty-two patients (39 women, 23 men; mean age 48 ± 17 years) fulfilled inclusion criteria.

10 with persistent cardiac arrest and 42 with severe shock.

14 patients were treated with ECLS and 48 patients with conventional therapies.

All subjects received vasopressor and fluid loading.
Survivors (%)

ECLS
n = 14

86 %

No ECLS
n = 48

48 %

p < 0.045 *
Question 6

• If you asked for extracorporeal life support in your institution and all agreed how quickly could you accomplish it?
  – 1 hour
  – Within 2 hours
  – Within 4 hours
  – Within 6 hours
  – Greater than 6 hours
Question 6

• If you asked for extracorporeal life support in your institution and all agreed how quickly could you accomplish it?
  – 1 hour
  – Within 2 hours
  – Within 4 hours
  – Within 6 hours
  – Greater than 6 hours
Methylene Blue in the Treatment of Refractory Shock From an Amlodipine Overdose

David H. Jang, MD, Lewis S. Nelson, MD, Robert S. Hoffman, MD
Summary (1)

• Fluid therapy is largely clinical
  – Although CVP trends may provide some support they are not definitive
• Vasoconstrictors should be avoided when myocardial contractility is impaired
• Atropine has limited utility
• Glucagon is not very useful in calcium channel blocker overdose
Summary (1)

• Research to help decide between high-dose insulin glucose therapy over intravenous fat emulsion is limited
• Mechanical life support (ECLS) seems reasonable when pharmacotherapy is failing
• New treatments (methylene blue) deserve further evaluation