Death and Pharmacologic Optimization of Organ Donors

A Review for Pharmacy Personnel

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Pharmacist & Technician Objectives

- Explain the pathophysiology of death
- List optimum parameters for serum sodium and urine output in adult organ donors
- Review the literature for hormone resuscitation of organ donors
- List 2 medications used for hormone resuscitation in adult organ donors
What is Death
Historical Perspective

• Brain Death:
  1968 Harvard Ad Hoc committee –”A definition of irreversible coma”. A way to decide when it is appropriate to withdraw support, developed to redefine death while the heart was still beating.

  1976 UK Conference of Medical Royal Colleges statement on brain death –guidelines, apnea testing and included brain stem as the center of brain function: without it, no life exists.

  1995 American Academy of Neurology (AAN) –evidence based review, clinical examination, practical apnea testing & validity confirmatory tests
Causes of Brain Death

- Normal
- Cerebral Anoxia
Brain Death Current Consensus

- Absent Cerebral Function
- Absent Brainstem Function
- Apnea
Declaration of Brain Death

- Coma
- Absence of motor response
- Absence of pupillary response / pupils midposition
- Absence of corneal reflexes
- Absence of gag reflex
Normal Brain Anatomy

Cerebral Cortex

Brain Stem

Reticular Activating System
Brain Stem

Midbrain

Cranial Nerve III

- pupillary function
- eye movement
Brain Stem

Pons

Cranial Nerves IV, V, VI

- conjugate eye movement
- corneal reflex
Brain Stem

Medulla

Cranial Nerves IX, X

- Pharyngeal (Gag) Reflex
- Tracheal (Cough) Reflex

Respiration
Physiology of Brain Death

- Progressive CNS ischemia occurs in a rostral to caudal fashion.
- Cerebral ischemia precipitates vagal activation leading to bradycardia / hypotension.
- Ischemic pons $\rightarrow$ mixed vagal & sympathetic response or Cushing reflex. Bradycardia & hypertension.
- Ischemia medulla $\rightarrow$ autonomic sympathetic surge to preserve CPP. Vasoconstrictive effect of autonomic storm compromises end organ perfusion.
Physiology of Brain Death

• Posterior Pituitary dysfunction → common with low levels of vasopressin. Clinically manifests as Diabetes Insipidus

• Anterior Pituitary dysfunction → more variable with decreases in T3, thyroxine T4, ACTH, TSH & HGH
Self Assessment Question

At the end of a brain death exam the pharmacy student in the room yells “He’s not dead, look he raised from the waist and his arms also spontaneously raised together.” What is the most likely explanation for this?

a. A tractor beam is helping the patient rise
b. The “Force of the Jedi” is raising the patient
c. The patient is displaying the Lazarus Phenomenon (rising from the dead)
d. Spinal reflexes are responsible for the movements
Optimization of Organ Donors

- Medical management of organ donors
  - Respiratory Status
  - Hemodynamic Status: intravenous fluids
  - Lung Protocol
  - Vasopressors and Inotropes
  - Thyroid Hormones
  - Corticosteroids
  - Hormone Resuscitation
Adult Donor Management Goals

- Sbp above 100 mmHg & MAP above 60 mmHg
- HR 60 – 100 bpm
- Temp > 97° F
- Serum sodium < 150 mEq/L
- Serum glucose 65 – 140 mg/dL
- Serum pH 7.35 – 7.45
- Urine output 0.5 – 1 ml/kg/hour
- 1 or fewer inotropic or vasopressor meds
Preservation of the Organ Donor – Medical Management

• Respiratory Status

Goals: pH 7.35 – 7.45, O₂ sat > 93%, PaO₂ > 90%

Interventions: Adjust Vent. Settings (TV 10-12 ml/kg, adjust FIO₂ & PEEP, suction pt prn, Obtain Chest-XR, check ABG, Perform O₂ challenge
Preservation of the Organ Donor – Medical Management

- Hemodynamic Status
  Goals: SBP > 100 mmHg, MAP > 60 mmHg, HR > 60 - 100 bpm
  Interventions: Arterial line, check electrolytes (Na), Check base excess, check I & O’s over previous 24 hrs, assess urine output, assess free water deficit, start vasopressor drip, obtain cardiac echo if possible heart donor
Preservation of Organ Donors

Maintenance intravenous fluids

0.9% Sodium Chloride, Lactated Ringers are commonly utilized
Others: \( \frac{1}{2} \) NS, \( \frac{1}{4} \) NS, D5W and Normosol-R

Common infusion rates: 100 – 300 ml /hour

Certain patients with polyuria: may replace urine output 1 : 1 therefore some very high fluids rates (+ boluses) may be required
<table>
<thead>
<tr>
<th></th>
<th>pH</th>
<th>Na</th>
<th>Cl</th>
<th>K</th>
<th>Osm</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plasma</strong></td>
<td>7.35 – 7.45</td>
<td>140</td>
<td>100</td>
<td>4.5</td>
<td>290</td>
<td></td>
</tr>
<tr>
<td><strong>Lactated Ringers</strong></td>
<td>6 – 7.5</td>
<td>130</td>
<td>109</td>
<td>4</td>
<td>273</td>
<td>Lactate 28</td>
</tr>
<tr>
<td>0.9% NaCl</td>
<td>4.5 - 7.0</td>
<td>154</td>
<td>154</td>
<td>0</td>
<td>308</td>
<td></td>
</tr>
<tr>
<td>0.45% NaCl</td>
<td>4.5</td>
<td>77</td>
<td>77</td>
<td>0</td>
<td>154</td>
<td></td>
</tr>
<tr>
<td>D5W</td>
<td>3.5 – 5.5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>252</td>
<td>Dextrose 50</td>
</tr>
<tr>
<td>Normosol-R</td>
<td>6.6 – 7.6</td>
<td>140</td>
<td>98</td>
<td>5</td>
<td>294</td>
<td>Mg 3, Acetate 27</td>
</tr>
</tbody>
</table>

Values are expressed in commonly utilized units
Preservation of the Organ Donor – Medical Management

- Hemodynamic Status

  Serum Na > 150 mmol/L change mIVF ½ NS
  Serum Na > 160 mmol/L change to ¼ NS or D5W
  Replace UOP with mIVF 1:1 ml per ml
  If dehydrated then give fluid bolus
Preservation of Organ Donors
Example Lung Protocol

• Naloxone 8 mg IVP x 1 dose
• Vecuronium 0.1 mg/kg IVP x 1 dose
• Albuterol MDI 8 puffs q4h prn wheezing
• Suction every 1 – 2 hours
• Turn every 1 – 2 hours
Naloxone

Pulmonary dysfunction following brain death has been theorized to potentially include endogenous release of opioids, increased vascular permeability, increased hydrostatic pressure and release of inflammatory mediators.

Retrospective study with 32 brain dead (BD) patients who received naloxone 8 mg IV x1 vs. 32 BD patients who did not receive naloxone.

Markham L et al. Improvement in pulmonary function following administration of naloxone in brain dead patients. World Transplantation Congress, Poster abstract 1106, July 2006, Boston, MA.
## Naloxone Study

<table>
<thead>
<tr>
<th></th>
<th>Naloxone</th>
<th>No Naloxone</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hearts txp</strong></td>
<td>16 (50%)</td>
<td>8 (25%)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Lungs txp</strong></td>
<td>22 (34%)</td>
<td>7 (11%)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Increase in PFR</strong></td>
<td>49.8</td>
<td>3.5</td>
<td>0.15</td>
</tr>
</tbody>
</table>

PFR = Initial to final increase in PAO$_2$ / FIO$_2$

Markham L et al. World Transplantation Congress, Poster abstract 1106, July 2006, Boston, MA.
Organ Donors

Vasopressors and Inotropes

• Approx. 80% of organ donors require vasopressor support & 25% of organ donors are lost during maintenance
• Goal: preventing decreased perfusion to tissues, vital organs, maintaining MAP / CO
• Choice of mIVF depends on serum sodium & glucose levels
• Dopamine was traditional vasopressor of choice
• Vasopressin is now considered a first line agent
• Phenylephrine, Epinephrine & Norepinephrine utilized if dopamine +/- dobutamine is inadequate
Arginine Vasopressin (AVP)

- AVP -for diabetes insipidus & found to lower vasopressor requirements in donors, due to its intrinsic vasoconstrictor activity.
- Higher AVP doses can cause severe vasoconstriction

Prospective study of 24 brain dead organ donors all on dopamine. Patients were randomized to either saline or low dose AVP (300 mUnits / kg / min)

Results: The AVP group showed an increase in BP with decreased vasopressor use (p < 0.001)

Arginine Vasopressin (AVP)

- Retrospective analysis of AVP treated children below 18 yo vs. age matched controls. Patients evaluated during brain death evaluation & organ function was assessed 48 hrs post transplant by independent surgeon / organ function criteria.

<table>
<thead>
<tr>
<th>Results</th>
<th>AVP used (n=34)</th>
<th>Controls (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ability wean/stop vasopressors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Dopamine</td>
<td>42%</td>
<td>38%</td>
</tr>
<tr>
<td>- Dobutamine</td>
<td>57%</td>
<td>0%</td>
</tr>
<tr>
<td>- Epinephrine</td>
<td>80%</td>
<td>0%</td>
</tr>
<tr>
<td>- Norepinephrine</td>
<td>100%</td>
<td>40%</td>
</tr>
<tr>
<td>- Alpha agonist</td>
<td>78%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Katz K et al. Resuscitation 2000; 47: 33-40
# Arginine Vasopressin (AVP)

<table>
<thead>
<tr>
<th>Results</th>
<th>AVP used</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average MAP</td>
<td>82 +/-21</td>
<td>71 +/- 16</td>
</tr>
<tr>
<td>Good organ recovery function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Kidney</td>
<td>79%</td>
<td>69%</td>
</tr>
<tr>
<td>- Liver</td>
<td>87%</td>
<td>95%</td>
</tr>
<tr>
<td>- Heart</td>
<td>90%</td>
<td>71%</td>
</tr>
</tbody>
</table>

AVP infusion rate varied from 1 to 8 units / hour

Katz K et al. Resuscitation 2000; 47: 33-40
Hormone Resuscitation (HR) Thyroid hormones

- Anterior pituitary dysfunction may result in lowered levels of thyroxine & T3 in the blood.
- Clinically manifested as rise in serum lactate and increasing base deficit. This leads to donor hemodynamic instability & continued need for vasopressor support.
- Benefits of thyroid hormone replacement
Earlier studies were conflicting

A retrospective review of donors from 1/2001 to 12/2005. Donors using T4 with those who did not were compared.

<table>
<thead>
<tr>
<th>Demographics / Results</th>
<th>T4 use (n= 96)</th>
<th>No T4 use (n= 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>32 +/- 14</td>
<td>38 +/- 21</td>
</tr>
<tr>
<td>Coagulopathy (%)</td>
<td>56</td>
<td>53</td>
</tr>
<tr>
<td>Cardiac ischemia (%)</td>
<td>34</td>
<td>21</td>
</tr>
<tr>
<td>Acidosis (%)</td>
<td>28</td>
<td>16</td>
</tr>
<tr>
<td>Neurogenic pulm edema (%)</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Diabetes Insipidus (%)</td>
<td>40</td>
<td>63</td>
</tr>
<tr>
<td>Organs/donor (all)</td>
<td>3.9 +/- 1.7*</td>
<td>3.2 +/- 1.7*</td>
</tr>
</tbody>
</table>

*p<0.05

Salim AM et al. Clinical Transplantation 2007; 21: 405-409
Hormone Resuscitation (HR) Corticosteroids

• A retrospective study on donors -1/1995 to 12/1995
Donors given Methylprednisolone (MP) compared with those who were not given MP.

Results

<table>
<thead>
<tr>
<th></th>
<th>MP Used (n= 80)</th>
<th>No MP used (n= 38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO$_2$/FiO$_2$ ratio</td>
<td>↑ 16 +/- 14*</td>
<td>↓ 34.2 +/- 14* *p &lt;0.05</td>
</tr>
<tr>
<td># procured lungs</td>
<td>25 / 80*</td>
<td>3 / 38*</td>
</tr>
</tbody>
</table>

Methylprednisolone (MP) dose was 15 mg/kg

Hormone Resuscitation (HR)

- Typical protocol utilized by LifeCenter:
  - Levothyroxine (T4) IV infusion at 10 mcg/hour
  - Methylprednisolone 15 mg/kg IV x1 or Hydrocortisone IV
  - Vasopressin IV infusion 0.5 to 4 units/hr, titrate to UOP, to prevent hypotension from fluid loss
Hormone Resuscitation (HR)

- United Network for Organ Sharing (UNOS) Critical Pathway for the Organ Donor HR:
  - Methylprednisolone 15 mg/kg IV x1 (repeat q24h prn)
  - Triiodothyronine (T3) 4 mcg bolus then CIV 3 mcg/hour
  - Vasopressin CIV at 0.5 to 4 units/hour, titrated to SVR 800 – 1200 dynes/sec-cm via PA catheter
  - Insulin CIV, titrate to BG 120 – 180 mg/dL
Hormone Resuscitation Effects on Organ Transplantation

Retrospective analysis of BD donors from 1/2000 to 9/2001

10,292 BD donors were analyzed: 701 received 3 drug HR and 9591 NHR donors received none.

BD = Brain dead, HR = hormone replacement, NHR = No hormone replacement

Rosendale JD et al. Aggressive pharmacologic donor management results in more transplanted organs. Clinical Transplantation 2003; 75: 482-487
## Hormone Resuscitation Effects on Organ Transplantation

Organs transplanted per donor for HR vs. NHR donors

<table>
<thead>
<tr>
<th></th>
<th>Age &lt; 40</th>
<th>Age &gt; 40</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Donor Type</strong></td>
<td><strong>Organs Txp / donor</strong></td>
<td><strong>Organs Txp / donor</strong></td>
</tr>
<tr>
<td>HR donor</td>
<td>4.2</td>
<td>3.1</td>
</tr>
<tr>
<td>NHR donor</td>
<td>3.8</td>
<td>2.5</td>
</tr>
<tr>
<td><strong>p value</strong></td>
<td><strong>&lt; 0.01</strong></td>
<td><strong>&lt; 0.01</strong></td>
</tr>
</tbody>
</table>

Rosendale JD et al. Aggressive pharmacologic donor management results in more transplanted organs. Clinical Transplantation 2003; 75: 482-487
Hormone Resuscitation Effects on Organ Transplantation

Rosendale JD et al. Aggressive pharmacologic donor management results in more transplanted organs. Clinical Transplantation 2003; 75: 482-487
Hormone Resuscitation Effects on Organ Transplantation

• The mean number of organs from HR donors (3.8) was 22.5% greater than that from NHR donors (3.1), p < 0.001.

• An additional 2,053 organs were calculated to have been recovered from 5,921 brain dead donors.

Rosendale JD et al. Aggressive pharmacologic donor management results in more transplanted organs. Clinical Transplantation 2003; 75: 482-487
Organ Donation Case Study

- DH 25 yom with self inflicted GSW to the head admitted to trauma service in the NSICU. Pt had initial GCS = 3.

- Patient with DI – AVP titrate to UOP < 200 ml/hour
- Na 174: mIVF changed to ½ NS
- Levothyroxine drip – 10 mcg/hour
- Methylprednisolone – 850 mg IV x1
- BG 232 mg/dL – Insulin drip IV
Organ Donation Case Study

- **DH Organs recovered:**

  *Heart* – txp into male with heart failure requiring dependence on LVAD
  *Lungs* – txp into male dependent on daily oxygen from interstitial lung disease
  *Liver* – saved life of a 13 yo girl with liver failure
  *1 Kidney + Pancreas* – txp to mother with ESRD from Type 1 DM
  *Kidney* – txp to woman requiring dialysis due to severe Htn
Self Assessment Question

• The United Network for Organ Sharing clinical pathway for organ donors includes which of the following three medications for HR?

a. Methimazole, Propranolol, D10W infusion
b. T3, Methylprednisolone, Vasopressin infusion
c. Nicardipine drip, Nitroprusside drip & Labetalol drip
d. Methylprednisolone drip, cefepime drip and tobramycin drip
Why Organ Donation?

• In the U.S.A about 115,000 people are waiting for a life saving transplant.
• In Ohio, nearly 3,500 individuals wait for a second chance at life.
• Every year about 6500 individuals die waiting for a transplant.
• Every 48 hours an Ohioan dies waiting for a transplant.

www.lifepassiton.org
Summary - Death and Preservation of Organ Donors

• Brain death has become medically accepted definition of death after the advent of mechanical ventilation
• Normalizing physiologic variables is the goal in the maintenance of organ donors
• Pharmacy personnel can play a vital role during the evaluation & maintenance of the organ donor by promoting appropriate therapy
ORGAN DONATION LINKS

www.lifepassiton.org  LifeCenter Organ Donor Network
www.unos.org  United Network for Organ Sharing
www.aopo.org  Association of Organ Procurement Organizations
www.donatelifeline.net  Donate Life America
www.cintieb.org  Cincinnati Eye Bank
www.donatelifedayo.org  Ohio organ donation sign-up
www.kyorgandonor.org  Kentucky organ donation sign-up
www.indianalastwishregistry.org  Indiana donation sign-up