Malignant Hyperthermia: Managing and Understanding Acute Episodes

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Objectives
• 1. Define malignant hyperthermia (MH)
• 2. Identify recommended MH treatment strategy
• 3. Summarize the role of a pharmacist in MH treatment
• 4. Memorize MH hotline phone number

Definition
• Rare but lethal pharmacogenetic condition triggered by volatile anesthetics and succinylcholine that results in a hypermetabolic state.
• Results in hypercarbia, hyperkalemia, and myoglobinuria that leads vital organ damage.
• Terminology = Malignant Hyperthermia Susceptible

Incidence and Mortality
• Occurs approximately in 1 in 5,000 – 10,000 children and 1 in 50,000 adult anesthesias
  – Historical mortality rate: 80%
  – Current mortality rate: < 10%
• Approach every patient as possibly being MHS.

Physiology of Muscle
**Mitigating Components**

- **Triggering Agents**
  - Inhalation anesthetics
    - Halothane, isoflurane, enflurane, sevoflurane, desflurane
  - Succinylcholine
  - Temperature
  - Stress

- **Genetic Factors**
  - De novo
  - Autosomal dominant inheritance
    - Results in 50% chance of passing it to offspring
  - Mutation Factors:
    - Mutations encoding the genes for RYR1 or DHP receptors

**Testing Methods**

- **In vitro contracture test (IVCT)**
  - Caffeine Halothane Contracture Test (CHCT)

- **Genetic Testing**
  - Alternative method

**Presentation of Early Signs/Symptoms**

- Onset of Presentation:
  - Anytime during anesthesia and post-operatively
  - Fulminant or indolent
  - Muscle Rigidity
    - Masseter muscle rigidity
    - Generalized rigidity
  - Hypercarbia
    - Rise in end-expired carbon dioxide concentration
  - Sinus Tachycardia
  - Tachypnea and Cyanosis

**Presentation of Late Signs/Symptoms**

- Fever and Sweating
  - Temperatures can be up to 113°F
- Myoglobinuria and cola colored urine
- Hyperkalemia
  - Cardiac Arrhythmias (V-tach or V-fib)
- Mixed respiratory and metabolic acidosis
- Excessive Bleeding

**Laboratory Values**

<table>
<thead>
<tr>
<th>Lab Parameter</th>
<th>Lab Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABG</td>
<td>pH &lt; 7.26</td>
</tr>
<tr>
<td>PaCO₂</td>
<td>&gt; 60 mmHg</td>
</tr>
<tr>
<td>PaO₂</td>
<td>&gt; 55 mmHg</td>
</tr>
<tr>
<td>H⁺</td>
<td>&gt; 8 nEq/L</td>
</tr>
<tr>
<td>Creatinine Kinase</td>
<td>&gt; 1,000, if inhaled anesthetic</td>
</tr>
<tr>
<td>Serum Myoglobin</td>
<td>&gt; 170 mg/dL</td>
</tr>
<tr>
<td>Urine Myoglobin</td>
<td>&gt; 200 mg/dL</td>
</tr>
</tbody>
</table>

**Differential Diagnosis**

- **Primary**
  - Hyperkalemic cardiac arrest in muscular dystrophy patients
  - Poor ventilation
  - Rhabdomyolysis
  - Neuromalignant Syndrome
    - Exact same presentation
      - rigidity, hyperthermia, acidosis, rhabdomyolysis
  - Drugs of abuse
- **Secondary**
  - Sepsis
  - Thyroid Storm
  - Pheochromocytoma
  - Iatrogenic overheating
  - Transfusion reaction from blood product
Therapy Goals

- Treatment must be emergent.
  - Administer once a diagnosis of MH is reasonable.

- Goals:
  - 1. Hyperventilate/Manage Hypercarbia
  - 2. Administer Dantrolene
  - 3. Treat Hyperkalemia
  - 4. Cooling to core temperature of 38° C

Acute MH Crisis Management

- 1. Stop the trigger agent
- 2. Purge the anesthesia machine with 100% O₂ at high rates
- 3. Alert the team and others to help
- 4. Administer dantrolene
- 5. Place activated charcoal in inspiratory and expiratory ports of machine
- 6. Place a foley and gain additional access
- 7. Cool the patient to 38° C

MH Cart Content

- Dantrolene
  - 36 vials
- Sterile Water
  - Room temperature or 35-40 °C
  - Vials v. bags debate
- Bicarbonate 8.4 %
- Dextrose 50 %
- Calcium Chloride 10 %
- Regular Insulin
- Lidocaine 2 % or Amiodarone
- Refrigerated saline

Goal 1 : Managing Hypercarbia

- Hypercarbia concerns:
  - Increase minute ventilation or increase tidal volume
  - Look for obstruction

  If this doesn’t solve the issue, then we have greatly increased or suspicion of MH and should initiate the treatment protocol.

Goal 2 : Initiate Dantrolene

- Hydantoin derivative developed as a muscle relaxant in 1973
  - Mechanism of action:
    - binds to the ryanodine receptor to deter the release of calcium from the sarcoplasmic reticulum.
  - Utilization of dantrolene in malignant hyperthermia discovered in 1975
  - Dr. Keith Ellis teamed with South African anesthesiologist Gaisford Harrison
  - Only available in PO formulation
  - IV formulation approved in 1979

Dantrolene Monograph

- Indications:
  - Malignant Hyperthermia
  - Chronic Spasticity
  - Tetanus*
  - Neuroleptic malignant syndrome*
  - Rhabdomyolysis*
  - MDMA toxicity*
  - Pharmacokinetics:
    - T_{max} IV: 1 minute
  - Storage:
    - Room temperature
    - Accessible from any GA area within 10 minutes
- ADRs:
  - Nausea
  - Diarrhea
  - Fatigue/Malaise
  - Flushing
  - Lightheadedness
  - Muscle weakness...
  - Respiratory muscle weakness...
- Blackbox warnings:
  - Hepatotoxicity
Dantrolene Products

- **Dantrium IV Rapid Mixing Powder for solution**
  - Lyophilized powder 20 mg vial with 3 g of mannitol
  - Sodium hydroxide \( \sim pH = 9.5 \)
  - DSM Pharmaceuticals
  - Cost: $65 / vial
- **Revonto IV Powder**
  - Lyophilized powder 20 mg vial with 3 g of mannitol
  - Sodium hydroxide \( \sim pH = 9.5 \)
  - JHP Pharmaceuticals
  - Cost: $92 / vial
- **Dantrium and generic oral capsule**

Dantrolene Administration

- **Dosing:**
  - LD: 2.5 mg/kg IV Push
    - Bolus doses: 1 mg/kg IV Push until symptoms subside
    - Max: 10 mg/kg IV Push
    - May require up to 30 mg/kg IV Push
  - Additional post-op doses required
- **Administration:**
  - Dissolve each with 60 mL of sterile water PF
  - Large bore IV line in largest central or peripheral line available

Supply Requirements

<table>
<thead>
<tr>
<th>Patient Weight</th>
<th>Dantrium Vials</th>
<th>Sterile H2O (mL)</th>
<th>Dantrolene Vials</th>
<th>Sterile H2O (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>kg</td>
<td>lb</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>110</td>
<td>62.5</td>
<td>575</td>
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<tr>
<td>70</td>
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<td>80</td>
<td>181</td>
<td>11.25</td>
<td>925</td>
<td>0.9</td>
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<tr>
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<td>242</td>
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<td>1255</td>
<td>1.1</td>
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<td>130</td>
<td>286</td>
<td>16.25</td>
<td>1575</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Goal 3: Treatment of Hyperkalemia

- Insulin + Glucose
  - 10 units IV and 60 mL of 10% dextrose
  - 0.1 units/kg IV and 0.8 mg/kg dextrose
  - Treat if K+ > 6.5 or ECG changes
- Calcium
  - Calcium chloride 10 mg/kg
  - Calcium carbonate 30 mg/kg
- Sodium bicarbonate 1-3 mEq/kg/dose
  - 10 mEq for base deficits > 8
- Furosamide 0.5-1 mg/kg IV once

- Consider atropine, lidocaine, diahydral or ECMO
- \( \text{Ca}^{2+} \) Calcium Channel Blockers

Goal 4: Supportive Care

- Hydration to protect the kidneys
- Cool to core temp
  - Infuse cooled saline
  - Lavage open body cavities
  - Nasogastric lavage
  - Ice the surface
  - Goal Core Temperature: < 38.5°C (101.3°F)
- Bladder catheterization
  - Monitor hemoglobin for myoglobinuria
  - Continue monitoring twice daily trends downward
Post-Op Management

- Continue dantrolene
  - Bolus dose: 1 mg/kg IV Q4-6H for 24 – 48H
  - Continuous infusion: 0.1 – 0.3 mg/kg/hr
  - Continue treatment of any symptoms or components of MH
- Transfer to ICU
  - Ventilation care
  - Hemodynamic monitoring for at lest 24 hours
  - Monitor for recrudescence
  - Monitor vitals and respiration continuously for 24 hours

Future General Anesthesia

- Utilize non-triggering anesthetics or local anesthetics
  - Local:
    - Spinal, epidural, and nerve block agents
    - Lidocaine, ropivacaine, bupivacaine, etc.
  - Alternative agents:
    - Nitrous oxide, pentobarbital, thiotetanal, propofol, diazepam, atropine, ketamine, propofol, cisatracurium
- If intubation is required:
  - Machine MUST be purged
  - Change circuits
  - Flush the machine at 10 L/min for 20 min
  - Constant temperature and capnography monitoring

Components of Success

- 1. Education
- 2. Kit Preparation
- 3. MHAUS Based Protocol
- 4. Periodic Drills
- Call the MH HOTLINE
  1-800-644-9737

References

14. SUNY Department of Anesthesiology. Anesthesiology knowledge – Malignant Hyperthermia. SUNY downstate website.