Therapeutic Hypothermia and Pharmacologic Considerations

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Disclosure Statement:

I have no financial or personal relationships with the commercial entities (or their competitors) that may be referenced in this presentation.
Objectives

- Review medication metabolism and clearance
- Describe effects that hypothermia has on drug pharmacodynamics/kinetics
- Discuss complications with therapeutic hypothermia and medication management options
ADME

Absorption

Distribution

Metabolism

Elimination
Metabolism

- CYP450 enzymes activate and detox many medications
- Medication metabolism during hypothermia
  - Kinetic properties of most enzyme systems are temperature dependent
  - Less medication binding to hepatic enzymes
  - Decreased affinity of medication for specific enzyme

P450 Metabolized Drugs

- Amiodarone
- Lidocaine
- Metoprolol
- Digoxin
- Diltiazem
- Midazolam
- Propofol
- Fentanyl
- Morphine
- Phenytoin
- Carbamazepine
- Pantoprazole
- Famotidine
- Vecuronium
- Verapamil
- Codeine
- Macrolides
- Fluoroquinolones
- Amlodipine
- Methylprednisolone
- Prednisone

Tortorici MA, et al. Cit Care Med 2007;35:2196-2204
Several ways the body eliminates medications:

- Hepatic elimination
- Renal clearance
- Biliary clearance

Hypothermia on Elimination

- Decrease in hepatic blood flow
- Decrease in biliary flow
- Renal Elimination?
  - Dependent on kidney blood flow and glomerular filtration rate
  - Passive transport so may not be affected in hypothermia
Drug Response to Hypothermia

Hypothermia

- Reduced Metabolism and Elimination of Drugs
- Altered Drug Response
- Reduced Doses
  - Increased Frequency
  - Monitoring for Toxicity and Efficacy
Complications Associated with Therapeutic Hypothermia

- Shivering
- Sedation
- Cardiovascular Effects
- Electrolyte disorders
- Hyperglycemia
- Infection
Core Body Temperature Change Response

- Sweating
- Vasodilation
- 37.5°C to 36.5°C Thermoneutral Zone
- Vasoconstriction
- Shivering
Shivering

- Natural response to reduction in body temperature
- Shivering threshold between 36°C and 33.5°C
- Why we want to counteract shivering:
  - 600% increase in metabolic heat production
  - Increased metabolic metabolism
  - Increased oxygen demand/consumption
  - Increased stress response

# Medications Used to Combat Shivering

<table>
<thead>
<tr>
<th>Medication</th>
<th>Effect on shivering</th>
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<tbody>
<tr>
<td>Paralytics</td>
<td>++++++</td>
</tr>
<tr>
<td>Meperidene</td>
<td>++++</td>
</tr>
<tr>
<td>Opiates (fentanyl/Morphine)</td>
<td>+++</td>
</tr>
<tr>
<td>Propofol</td>
<td>+++</td>
</tr>
<tr>
<td>Clonidine</td>
<td>+++</td>
</tr>
<tr>
<td>Benzodiazapines</td>
<td>++</td>
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<tr>
<td>Magnesium</td>
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# Paralytics (pro/con)

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
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<tbody>
<tr>
<td>- Effective</td>
<td>- Masks insufficient sedation</td>
</tr>
<tr>
<td>- Does not cause hypotension</td>
<td>- Masks seizure activity</td>
</tr>
<tr>
<td>- Leads to more rapid cooling</td>
<td>- Polyneuromyopathy in prolonged paralysis</td>
</tr>
</tbody>
</table>

*Weant KA, et al. Pharmacotherapy 2010;30(8):830-81*

*Polderman KH, Ingeborg H. Crit Care Med 2009;37:1101-1120*
# Paralytics Used in Hypothermia

<table>
<thead>
<tr>
<th>Medication</th>
<th>Onset</th>
<th>Duration of Action (DOA)</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Vecuronium | 180 sec | 33 min                  | • Metabolized by P450 enzymes  
• **3-fold increase in DOA with hypothermia** |
| Rocuronium | 75 sec  | 33 min                  | • Primarily eliminated in bile  
• **2-fold decrease in systemic clearance** |
| Atracurium | 110 sec | 43 min                  | • Hofman elimination  
• **1.5-fold increase in DOA** |

Shivering Management

**Meperidine:**

- **Benefits:**
  - Opiate with best data on decreasing shivering threshold

- **Cons:**
  - Large doses needed when used as monotherapy
  - Metabolized to active metabolite (normeperidine)
  - Adverse Effects:
    - Hypotension
    - Myoclonus
    - Seizure activity

Shivering Management

Fentanyl:

- Potent opiate with quick onset
- Mild hypotensive response
- Metabolism by P450 enzymes which decreases clearance in hypothermia

Morphine:

- Histamine release/vasodilation/hypotension
- Decreased potency/response in hypothermia
Shivering Management

**Propofol:**

- **Benefits:**
  - Fast onset/offset
  - Decreases cerebral metabolic oxygen consumption
  - Decreases shivering threshold

- **Cons:**
  - Causes hypotension and bradycardia
  - Metabolized through hepatic P450 and glucuronidation
  - Hypothermia shown to increase propofol concentration ~30%

Shivering Management

**Alpha₂ Agonists (dexmedetomidine and clonidine):**

- Alpha₂ adrenergic actions on central thermoregulatory centers
- **Benefits with dexmedetomidine:**
  - Fast acting sedative with analgesic properties
  - Decreases both vasoconstriction and shivering thresholds
- **Cons:**
  - Hypotension and bradycardia

Shivering Management

Magnesium:

Benefits:
- Combats vasoconstriction
- May have neuroprotective properties
- Shown to decrease time to target temperature and patient comfort

Cons:
- No sedative or analgesic properties
- Little benefit when used as sole agent

Shivering Management

**Combination Therapy:**

- Utilizes different antishivering mechanisms of action
- Maximize effect on shivering threshold
- Decrease doses = decrease adverse effects
- Buspirone reduces shivering

Shivering Management

Non-Pharmacologic Methods:

- Surface Counterwarming
  - Warming of the face, hands, feet

Shivering Conclusion

- Common physiologic response to hypothermia
- Data showing shivering can be controlled with deep sedation
- Paralytic use may be first line option during induction phase and last line option during maintenance phase
- Combination therapy
Sedation

- All patients need to receive some form of sedation
- Minimizes anxiety/discomfort and stress response
- Aids in the cooling process
- Lower doses, rates, and/or longer duration between doses
Electrolyte Disorders

- Magnesium, Potassium, Calcium, and Phosphorus
- “Cold-diuresis”
- Intracellular shift
- Magnesium prevents further brain injury
- Low Magnesium and Potassium = dysrhythmias
Electrolyte Management

- Pre-emptive magnesium supplementation
- Initiate potassium replacement if level < 4 mEq/L
- Frequent monitoring during therapeutic hypothermia
- Consider holding during rewarming phase
Cardiovascular Effects

- Initial tachycardia then bradycardia
- Arrhythmias rare at temperature >30°C
- Management of arrhythmias
  - Fluid balance
  - Electrolyte balance (Magnesium and Potassium)
  - Less responsive to anti-arrhythmics

Arpino PA, Greer DM. Pharmacotherapy 2008;28(1):102-111
Hyperglycemia

- Decrease insulin sensitivity AND secretion
- Increased gluconeogenesis and glycogenolysis
- Hyperglycemia associated with negative effect on neurologic outcomes
- Insulin drip for management
- Insulin sensitivity may increase rapidly during rewarming

Arpino PA, Greer DM. Pharmacotherapy 2008;28(1):102-111
Infection

- Hypothermia induced suppression:
  - Masking fever
  - Immune system
  - Neutrophil and macrophage activity
  - Secretion of proinflammatory cytokines

- Most common infections:
  - Wound & pneumonia (aspiration)

- Consider prophylactic antibiotics

Arpino PA, Greer DM. Pharmacotherapy 2008;28(1):102-111
Pharmacokinetic Summary

- Metabolism through CYP enzymes reduced during therapeutic hypothermia
- Clearance of medications and metabolites decreases during hypothermia
- Medication dosing not specific but may require lower doses
- Increased frequency between doses to avoid side effects or toxicity
Summary of Complications

- Utilize combination therapy to manage shivering response

- Proactive/aggressive management of electrolyte and glycemic imbalances during induction/maintenance

- Prophylactic antibiotic therapy if infection suspected

- Careful and frequent monitoring

- Management to change with re-warming phase!!
Questions