Tip of the Iceberg: Alterations of PK/PD in Patients Undergoing Targeted Temperature Management

A presentation for HealthTrust Members

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Speaker Disclosures

• The presenter has no real or perceived conflicts of interest related to this presentation.

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Learning objectives

• Compare pharmacokinetic parameters for normothermic and hypothermic patients

• Select monitoring parameters appropriate for targeted temperature management

• Identify medications likely to require adjustment due to targeted temperature management
Some Chilling Statistics

• 320,000 out-of-hospital cardiac arrests (OHCA) annually in the United States
  • 23% of these present with a shockable rhythm
  • Non-shockable rhythms have a poorer prognosis
• Remains a poor prognosis, survival to discharge in only ~7 – 11% of patients with OHCA and ~25% of patients arresting within the hospital

An icebreaker with targeted temperature management (TTM)

- Currently debated if the benefit is driven by therapeutic hypothermia (TH) vs. prevention of fever following cardiac arrest
  - Early trials showing benefits of TH allowed control group to become febrile
  - Terminology has shifted from TH to TTM
- Lack of reproducibility and conflicting evidence has led to an overall decline in the use of TTM
  - Clinicians overall unfamiliar with TTM
  - Opportunities for improvement in pharmacotherapy

Induction
• Rapidly reducing core temperature to a goal of 32 - 36°C

Maintenance
• Remaining at goal temperature for 12 – 24 hours

Rewarming
• Gradual increase to normothermia over 12 – 24 hours

Overview of TTM

• Hypothermic state decreases production of free radicals, preserving long-term neurologic function

• TTM has demonstrated improved neurological outcomes following cardiac arrest in patients cooled to a goal temperature of 32 - 36°C (89.6 – 96.8°F) for 12 – 24 hours
  • Best studied in patients remaining comatose, following return of spontaneous circulation (ROSC) following advanced cardiac life support (ACLS) interventions, initially presenting with a shockable rhythm (pulseless ventricular tachycardia or ventricular fibrillation)

Pharmacokinetics & TTM

• Pharmacokinetics describes how drugs are absorbed, distributed, metabolized & excreted by the body

• Hypothermia has the potential to impact each of these phases, resulting in significant clinical effects

• An example of a drug-therapy interaction

• Overall lack of literature describing optimal medication changes in TTM

Absorption

• IV administration **bypasses** the absorption phase
  • May be considered the route of choice when possible for patients

• While not well characterized, it is expected that gut absorption is impaired during TTM secondary to increased transit times
  • Oral or rectal routes of administration are unreliable

• Little data exists examining alterations in subcutaneous, transdermal, and intramuscular routes of administration

A variety of physiological changes alter drug distribution, making generalization of effect difficult.

Examples of physiologic changes that must be taken into consideration:

- Altered blood flow, blood shunting to vital organs
- Blood pH decreases at lower temperatures
  - CO2 partial pressure increases
- Protein binding is altered
  - It may be increased, decreased, or unchanged depending on the drug
- Lipophilic penetration and tissue binding is decreased

Distribution

• Changes in vasodilatation and decreases in cardiac output have not been consistently proven to decrease volume of distribution at temperatures of 32 - 36°C

• Active transporters such as ABCB1 (P–glycoprotein) have exhibited decreased activity at 32°C
  • Typically, these pumps efflux drugs out of the cell, into a biological lumen for elimination
  • In vitro digoxin clearance was decreased by 50% in a study conducted by Jin et al.

Metabolism

- Decreased hepatic blood flow
- Decreased enzymatic activity
  - Prodrugs are less effective (decreased transformation)
  - Decreased breakdown of drugs to inactive metabolites
- Hepatic extraction ratio \( (E_H) \) describes drug concentration pre- and post- hepatically
  - \( E_H = (C_a - C_v)/C_a \)
    - \( C_a \) is the concentration in the hepatic arterial and mixed venous
    - \( C_v \) is the concentration in the hepatic venous blood
  - High extraction ratio (>0.7) are most altered by changes in blood flow
- Favorable to avoid drugs with hepatic metabolism

## Metabolism

<table>
<thead>
<tr>
<th>Drug</th>
<th>Elimination Half-Life</th>
<th>Hepatic Extraction Ratio</th>
<th>Cytochrome P450 Metabolism</th>
<th>Renal Elimination</th>
<th>Transporters</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General anesthetics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propofol</td>
<td>30–60 min</td>
<td>High</td>
<td>2B</td>
<td>Yes</td>
<td>UDP-glucuronosyltransferase</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>2–2.67 hr</td>
<td>High</td>
<td>2A6</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td>Midazolam</td>
<td>1.8–6.4 hr</td>
<td>Low/intermediate</td>
<td>3A4</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td><strong>Opioids</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>2.5–6.5 min</td>
<td>High</td>
<td>3A4</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>3–10 min</td>
<td>n/a</td>
<td>n/a</td>
<td>Yes</td>
<td>n/a</td>
</tr>
<tr>
<td>Meperidine</td>
<td>2.5–4 hr</td>
<td>High</td>
<td>none</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td><strong>Nonopioids</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>2 hr</td>
<td>Intermediate/high</td>
<td>2E1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td>Buspirone</td>
<td>2–3 hr</td>
<td>High</td>
<td>3A4</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td><strong>Paralytics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vecuronium</td>
<td>51–80 min</td>
<td>Low</td>
<td>3A4</td>
<td>Yes</td>
<td>p-glycoprotein</td>
</tr>
<tr>
<td>Atracurium</td>
<td>20 min</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>None</td>
</tr>
</tbody>
</table>

<sup>a</sup>Cytochrome P4502E1 metabolizes acetaminophen to N-acetyl-p-benzoquinone imine, which is then inactivated by glutathione conjugation.

Antishivering activity qualification, as in reduction of shivering threshold: 1 (<i>0.2</i>°C), 3 (<i>0.2</i>–0.4°C), 5 (<i>0.5</i>–0.9°C), 7 (<i>0.9</i>–0.9°C).

**Drugs Affected by P-glycoprotein**

<table>
<thead>
<tr>
<th>Substrates</th>
<th>Inducers</th>
<th>Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin</td>
<td>Rifampin</td>
<td>Amiodarone</td>
</tr>
<tr>
<td>Loperamide</td>
<td>Carbamazepine</td>
<td>Ketoconazole</td>
</tr>
<tr>
<td>Colchicine</td>
<td>Phenytoin</td>
<td>Clarithromycin</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Dexamethasone</td>
<td>Cyclosporine</td>
</tr>
<tr>
<td><strong>Morphine</strong></td>
<td></td>
<td>Verapamil</td>
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<tr>
<td></td>
<td></td>
<td>Quinidine</td>
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<tr>
<td></td>
<td></td>
<td>Ritonavir</td>
</tr>
</tbody>
</table>

- This list is generalized and not specific to TTM, some studies report conflicting results about the effect of hypothermia on specific drugs such as quinididine.
- Decreases in Pgp activity will cause higher uptake of drug into cells.
Excretion

- Tubular secretion and reabsorption are enzyme-dependent processes
  - May be decreased in hypothermia
- Cold-induced diuresis has been described
  - Vasoconstriction from cold causes diuresis
- Decreases in renal clearance have not been consistently described
  - Creatinine synthesis is decreased
  - Cockcroft-Gault estimation may be unreliable

Which of the following pharmacokinetic parameters are likely to be decreased in a patient undergoing targeted temperature management in an ICU setting? (Select all that apply)

- A: Absorption
- B: Distribution
- C: Metabolism
- D: Excretion
Which of the following pharmacokinetic parameters are likely to be decreased in a patient undergoing targeted temperature management in an ICU setting? (Select all that apply)

- A: Absorption
- B: Distribution
- C: Metabolism
- D: Excretion
General Goals of Pharmacotherapy in TTM

• Prevention of **shivering**
  • Managed with neuromuscular blockade & medications with anti-shivering effect

• Maintain deep level of **algosedation**
  • Titrate sedatives to a goal Richmond Agitation-Sedation Scale (RASS) of -5
  • Use of validated pain scoring systems to prevent long-term complications of pain
    • Critical-Care Pain Observation Tool (CPOT)
    • Behavioral Pain Scale (BPS)

Shivering

- Body’s natural attempt to rewarm patient
  - Adaptive response to cold
    - Stimulated at 35.5°C, ceases at 33.5°C
    - May occur during induction or rewarming of patient
  - Shivering upon induction associated with better neurological outcomes
  - May undermine efforts to keep patient cool
- No single drug can be administered at safe, effective doses to reduce shivering threshold
  - Combinations must be used
  - Examination of individual drugs is warranted in TTM to determine a preferred standard

Snow Day! Opioids for Shivering

• Decrease shivering threshold
• Dose often limited by respiratory depression
• Anti-shivering effect best characterized with meperidine
  • Reduces shivering threshold by ~ 2°C
  • Acts synergistically with buspirone
  • Active metabolite: normeperidine
    • Risk of neurotoxicity
• Remifentanil has potent anti-shivering effect
• Fentanyl has a minor anti-shivering effect
  • Class effect can not be assumed for opioids

Non-opioids for Shivering

• Clonidine & dexmedetomidine (α2 agonists) both reduce shivering threshold
  • Dexmedetomidine clearance reduced by ~60% in hepatic impairment, unknown if this is seen in TTM
• Acetaminophen decreases the hypothalamic resting point for temperature homeostasis
  • Reductions of 0.2 – 0.4°C seen with 3g and 6g doses
• Buspirone
  • 5HT1A partial agonism thought to provide anti-shivering effect
  • Typically given as 30mg po q8h
    • Studied in healthy male volunteers
    • Reduced shivering threshold by ~0.8°C

Paralytics for Shivering

• A well characterized, prolonged duration of action regardless of metabolic route

• Initial dose reductions of 25 – 50% should be implemented to prevent a prolonged duration of action

• Train-of-four (TOF) monitoring is shown to be altered in TTM
  • During rewarming, patients exhibit resistance to paralytic effects
  • Ex: TOF 4/4 despite same dose of paralytic during maintenance

## Anti-shivering Efficacy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Anti-shivering activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paralytics</td>
<td>++++</td>
</tr>
<tr>
<td>Meperidine</td>
<td>+++</td>
</tr>
<tr>
<td>Propofol</td>
<td>+++</td>
</tr>
<tr>
<td>Fentanyl, morphine</td>
<td>+++</td>
</tr>
<tr>
<td>Clonidine</td>
<td>+++</td>
</tr>
<tr>
<td>Doxapram, nefopam</td>
<td>+++</td>
</tr>
<tr>
<td>Midazolam</td>
<td>++</td>
</tr>
<tr>
<td>Magnesium</td>
<td>++</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>++</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>+</td>
</tr>
</tbody>
</table>

Paralytics Monitoring

• TOF monitoring is unreliable in TTM
• Titrate paralytics to clinical endpoints
  • Reduction of shivering response
  • Improved ventilator synchrony
• Intermittent boluses of paralytics are appropriate during rewarming
  • Avoidance of supratherapeutic concentrations
  • Shivering less likely to occur during maintenance, continuous infusions may not be needed
  • Excessive blockade may delay neuroprognostication

Bedside Shivering Assessment Scale (BSAS):

0 – None: No Shivering
1 – Mild: Shivering localized to neck/thorax, may be seen only as artifact on ECG or felt by palpation
2 – Moderate: Intermittent involvement of the upper extremities +/- thorax
3 – Severe: Generalized shivering or sustained upper/lower extremity shivering

• Validated 4 point scale used to assess shivering
• Columbia anti-shivering protocol proposes maintaining BSAS ≤ 1 during induction

Assessment question #2:

• Which of the following monitoring parameters is unreliable in a patient undergoing TTM?
  • A: Vancomycin trough level
  • B: TOF monitoring for paralytics
  • C: Blood glucose for patients receiving insulin
  • D: Serum creatinine
Assessment response #2:

• Which of the following monitoring parameters is unreliable in a patient undergoing TTM?
  • A: Vancomycin trough level
  • B: TOF monitoring for paralytics
  • C: Blood glucose for patients receiving insulin
  • D: Serum creatinine
Desirable Drug Qualities

• Short, predictable half life
  • Rapid onset & off-set

• Smaller volume of distribution
  • Less tissue penetration, more predictable kinetics

• Ease of monitoring
  • Monitoring for safety and efficacy of medication
Columbia Anti-Shivering Protocol

• Recommends baseline medications plus a stepwise approach to shivering management

• Baseline medications:
  • Acetaminophen 650 – 1000 mg q4-6h
  • Buspirone 30 mg q8h
  • Magnesium sulfate 0.5-1 mg/h IV
    • Goal magnesium level: 3 – 4 mg/dL
  • Skin counter warming at a maximum of 43 °C

Columbia Anti-Shivering Protocol

• First line: dexmedetomidine or opioids
  • Dexmedetomidine preferred for patients with underlying agitation
    • Dexmedetomidine 0.2 – 1.5 mcg/kg/hr
  • Opioids preferred for bradycardia or hypotensive patients
    • Fentanyl 25 mcg/hr or meperidine 50 – 100 mg IM/IV

• Second line: dexmedetomidine + opioids

• Third line: deep sedation with propofol

• Fourth line: neuromuscular blockade
  • This protocol prefers vecuronium (0.15mg/kg IV bolus)

Propofol vs. Midazolam

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Midazolam</th>
<th>Propofol</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed awakening, n (%)</td>
<td>56 (29%)</td>
<td>5 (6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ventilator free days at 28 days, n(IQR)</td>
<td>24 (22-26)</td>
<td>25 (22-26)</td>
<td>0.007</td>
</tr>
<tr>
<td>Pneumonia &gt;48 hours post admission, n (%)</td>
<td>65 (20%)</td>
<td>28 (21%)</td>
<td>0.82</td>
</tr>
<tr>
<td>Duration of sedation, hours median (IQR)</td>
<td>34 (30-41)</td>
<td>40 (31 – 54)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Renal replacement therapy, n(%)</td>
<td>151 (46%)</td>
<td>36 (27%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

- Propofol/remifentanil (n=134) versus midazolam/fentanyl (n=326) for sedation of patients during TTM following cardiac arrest
  - Retrospective study using prospectively collected data
  - Management protocol only differed in sedatives and neuromuscular blocker used
- Awakening: three consecutive RASS scores ≥ -2
- Delayed awakening: persistent unconsciousness ≥ 48 hours post sedative discontinuation

Propofol

- Studied in 2 women and 4 men on two different study visits with induced core hypothermia (to a targeted 34°C) on one of the two visits.
- Blood was sampled from radial arterial catheter to determine propofol concentrations over 2 hours via HPLC.
- Propofol concentrations were increased in hypothermic patients.
  - Largely driven by a decreased intercompartmental clearance.

Propofol

• Propofol concentrations increased in hypothermic patients
• Anticipate decreases in the required doses to maintain sedation goals
• Largest differences observed in the first 5 minutes of drug administration
• Drug did not distribute as well in the hypothermic patients

Midazolam

- A dangerous kinetic recipe
  - Large volume of distribution
  - High hepatic extraction ratio
    - Active metabolite
- Hostler et al. modeled midazolam kinetics in 6 healthy subjects aged 19 – 39 with no known comorbidities infused with cold saline for 4 hours
  - Identified changes in midazolam clearance when hypothermia was induced
  - Predicted an **11% decrease in midazolam clearance for every 1°C decrease in core temperature from 35.5°C**

Fentanyl

• Commonly used in ICU settings to manage pain
  • Used in TTM to prevent shivering

• Extensively metabolized by CYP3A4
  • Well-stirred PK model predicts that decreased hepatic blood flow expected to cause a decrease in clearance, difficult to quantify changes
  • Bjelland et al. reported a 46% decrease in fentanyl clearance in 14 hypothermic patients matched to 8 normothermic controls

• Should be started at lower doses (25mcg/hr) to avoid overdosing & delayed awakening
Other TTM Considerations

• Cardiac output decreases
  • Initial rise in BP from vasoconstriction
  • Eventual decrease in output following cold diuresis
  • Oxygen demand and consumption also decreases
  • No effect on MAP
  • Heart rate slows
    • QTc prolongation is commonly observed (reports up to 670ms!)
    • Well documented safety of QTc prolongation during TTM

• Evidence supports the following hemodynamic parameters to improve neurologic outcomes:
  • MAP >65 mm Hg
  • CVP >15 mm Hg
  • permissive bradycardia (31 – 48 bpm)

Vasopressor use in TTM

- 920 patients analyzed in multicenter study at 36 ICUs in 10 countries from the Target Temperature Management trial
  - ↑lactate, similar MAP, ↓HR observed in TTM group versus normothermic group
  - Lower MAPs were associated with increases in mortality
- Increased doses of vasopressors were observed in TTM group
  - Data regarding specific vasoactive agents used was not available
  - Higher doses of vasopressors was associated with increased mortality at 30 days, but difference was not statistically significant
- Vasoactive agents without chronotropic activity should be utilized to meet these goals (phenylephrine)
  - May avoid arrhythmia while maintaining MAP

Bleeding Diathesis

• Hypothermia not recommended in actively bleeding patients
  • Relative contraindication

• Lower temperatures decrease activity of coagulation cascade
  • aPTT/PTT samples should be analyzed at 32 or 34 °C to reflect in vivo activity

• Bleeding is a enzymatic-dependent process effected by hypothermia
  • Elevated aPTTs are commonly observed

Bleeding Diathesis

• Anticoagulation may be necessary depending on cause of cardiac arrest; ie: pulmonary embolism, myocardial infarction
  • Unfractionated heparin (UFH) preferred over low molecular weight heparins
  • UFH has a shorter half-life and is easily reversible with protamine
• Heparin has a saturable metabolism and clearance that is likely decreased in hypothermia
  • Wahby et al. found only 3/46 patients achieving goal aPTT following initial dosing of UFH
    • Dose was lower than standard dose for all 3 of these patients
    • Only 10/46 patients (22%) had therapeutic aPTT at 24 hours
• Heparin rates expected to return to standard protocol ~24 hours after cessation of TTM

Bleeding Diathesis

• Antiplatelet agents are commonly given as part of ACS and PCI treatment algorithms
  • Clopidogrel is a prodrug requiring GI absorption and liver metabolism to become pharmacologically active
    • Both processes are decreased in TTM
    • Kaufmann et al. found a decrease in plasma concentration of clopidogrel and metabolites in TTM group versus normothermic group that were given 600mg as a loading dose for patients undergoing PCI
  • Aspirin is a highly protein bound drug that exhibited decreased effect (most pronounced at 72 hours) in a study conducted by Pruller et al.
    • Reduced GI absorption, accelerated platelet turnover in inflammatory states may explain decreased efficacy

• Patients may remain at significant risk for acute stent thrombosis due to decreased efficacy of antiplatelet therapies

Electrolyte Disturbances

- Increase risk of arrhythmias if uncorrected
- Hypokalemia and hypomagnesemia are common complications of TTM that should be anticipated
  - Possibly due to increased renal excretion
- Beaulieu et al. found that 98% of patient experienced hypokalemia during TTM
  - Median of 45 mEq of potassium given each day
  - 30% of patients remained hypokalemic despite repletion
  - 2% of patients became hyperkalemic
- Standard potassium repletion strategies may not be effective in TTM

Electrolyte Disturbances

• Some studies have observed hypokalemia is especially pronounced during induction phase
  • Effect is not consistent across all studies
• Hypomagnesemia may potentiate hypokalemia or prevent successful repletion
• Hypomagnesemia observed less frequently than hypokalemia
  • IV magnesium typically given as part of TTM protocol

Summary

• Use of IV administration bypasses GI absorption issues
  • GI absorption is decreased
• Distribution will likely be decreased
• Metabolism will likely be decreased
• Drugs with predictable kinetics are preferred
  • No hepatic clearance or metabolites
  • Low - intermediate volume of distribution
  • Short acting
• TOF, aPTT, PTT monitoring will be altered and potentially unreliable throughout TTM
Assessment question #3:

- Which of the following medications would likely require a dosage adjustment during TTM?
  - A: Fentanyl
  - B: Rosuvastatin
  - C: Famotidine
  - D: Trimethoprim/sulfamethoxazole
Assessment response #3:

- Which of the following medications would likely require a dosage adjustment during TTM?
  - A: Fentanyl
  - B: Rosuvastatin
  - C: Famotidine
  - D: Trimethoprim/sulfamethoxazole
References


Thank you!!

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