Therapeutic Hypothermia and Pharmacologic Considerations

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Disclosures

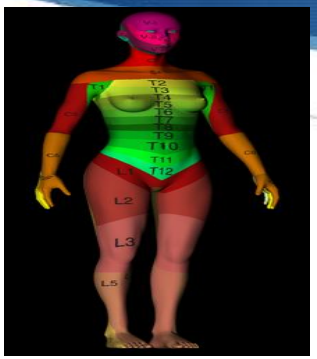
Disclosure Statement:

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



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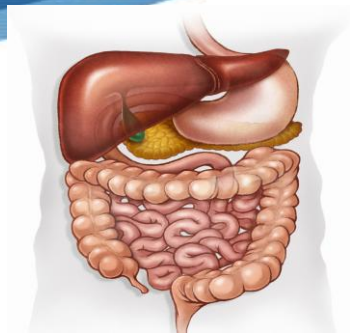
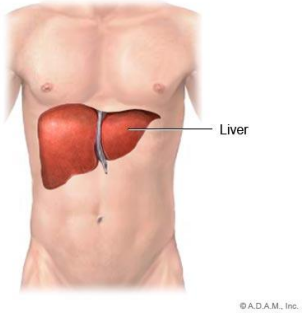


Absorption

ADME



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

Tortorici MA, et al. Cit Care Med 2007;35:2196-2204

P450 Metabolized Drugs

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

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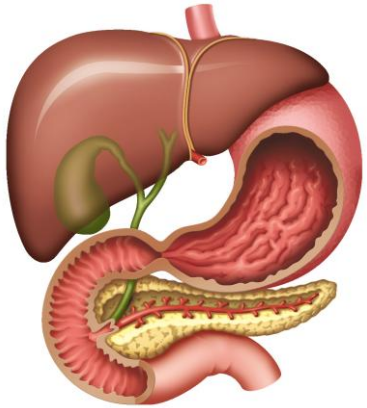
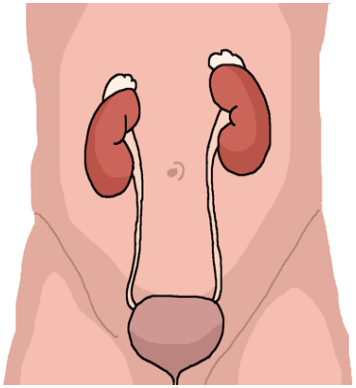
Elimination

- Several ways the body eliminates medications:
  - Hepatic elimination
  - Renal clearance
  - Biliary clearance





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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

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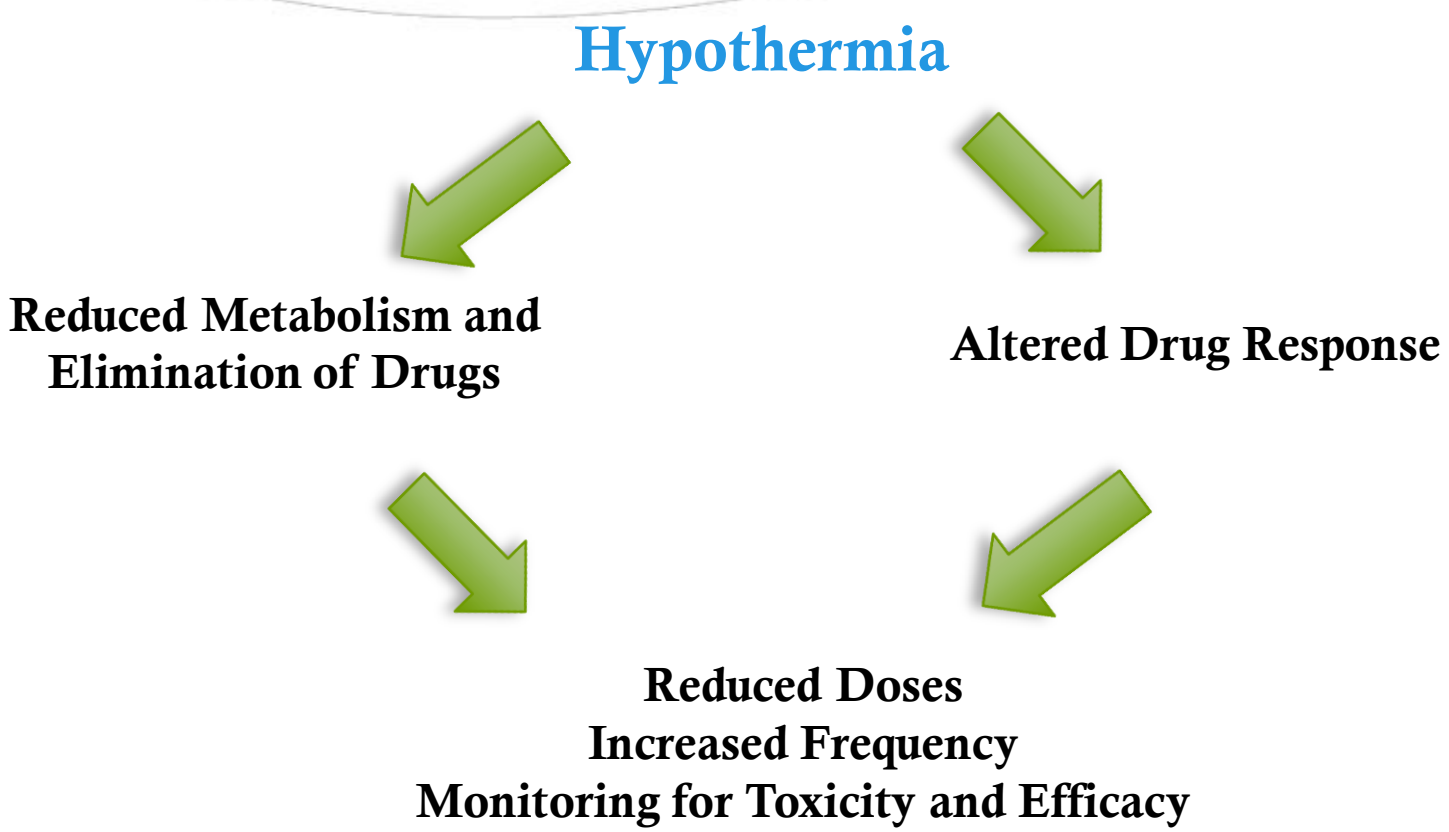
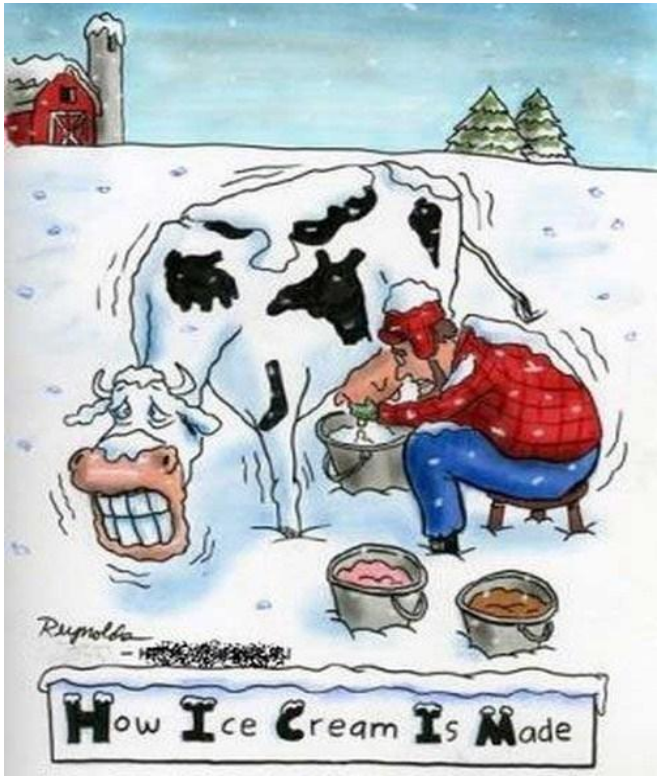
Drug Response to Hypothermia



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
Thermoneutroal 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

Weant KA, et al. Pharmacotherapy 2010;30(8):830-841

Medications Used to Combat Shivering

Medication	Effect on shivering
Paralytics	+++++
Meperidine	++++
Opiates (fentanyl/Morphine)	+++
Propofol	+++
Clonidine	+++
Benzodiazapines	++
Magnesium	++

Polderman KH, Ingeborg H. Crit Care Med 2009;37:1101-1120

Paralytics (pro/con)

Pros	Cons
Effective	Masks insufficient sedation
Does not cause hypotension	Masks seizure activity
Leads to more rapid cooling	Polyneuromyopathy in prolonged paralysis

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

Medication	Onset	Duration of Action (DOA)	Comments
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**

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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

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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

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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%

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Shivering Management

<u>Alpha$_2$ Agonists (dexmedetomidine and clonidine):</u>

- Alpha$_2$ adrenergic actions on central thermoregulatory centers
- <u>Benefits with dexmedetomidine:</u>
  - Fast acting sedative with analgesic properties
  - Decreases both vasoconstriction and shivering thresholds
- <u>Cons:</u>
  - Hypotension and bradycardia

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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

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Polderman KH, Ingeborg H. Crit Care Med 2009;37:1101-1120

Shivering Management

Combination Therapy:

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

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Shivering Management

Non-Pharmacologic Methods:

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

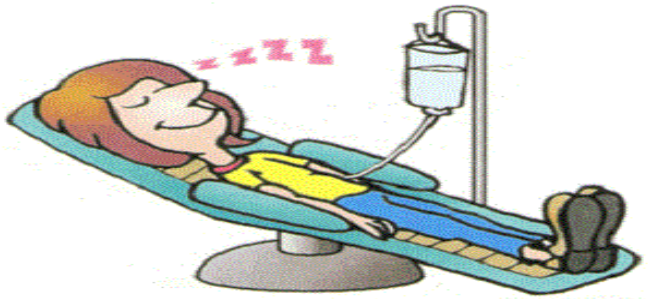
Lee R, Asare K. Am J Health-Syst Pharm 2010;67:1229-37

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



Wiggins BS, Sanoski CA. American Society of Health-System Pharmacists 2012 edition

Electrolyte Disorders

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

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

Electrolyte Management

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

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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

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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

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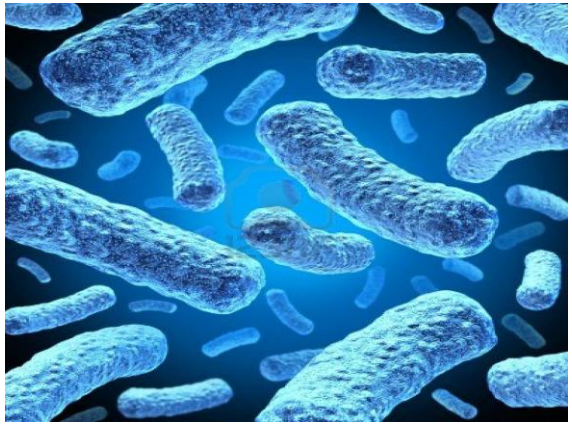
Infection

- Hypothermia induced supression:
  - Masking fever
  - Immune system
  - Neutrophil and macrophage activity
  - Secretion of proinflammatory cytokines
- Most common infections:
  - Wound & pneumonia (aspiration)
- Consider prophylactic antibiotics



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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