

Therapeutic Hypothermia and Pharmacologic Considerations

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August 6, 2013



Disclosures

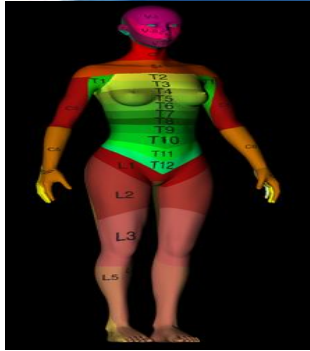
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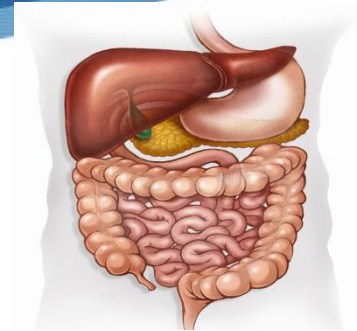
Objectives

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

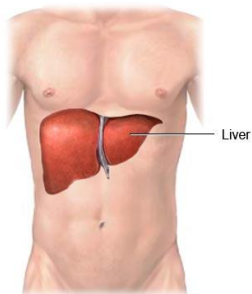
ADME



Distribution



Absorption



Liver

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Metabolism



Elimination

Metabolism

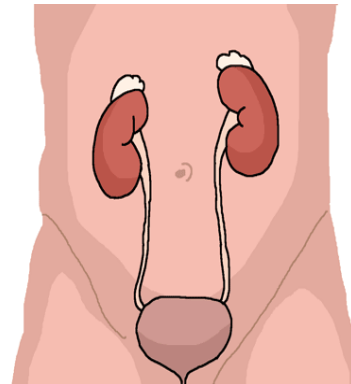
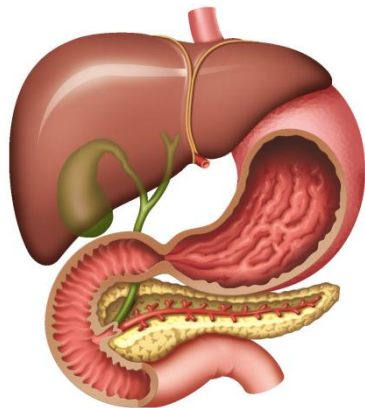
- ◆ CYP450 enzymes activate and detox many medications
- ◆ Medication metabolism during hypothermia
 - ◆ Kinetic properties of most enzyme systems are temperature dependent
 - ◆ Less medication binding to hepatic enzymes
 - ◆ Decreased affinity of medication for specific enzyme

P450 Metabolized Drugs

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

Elimination

- ◆ 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

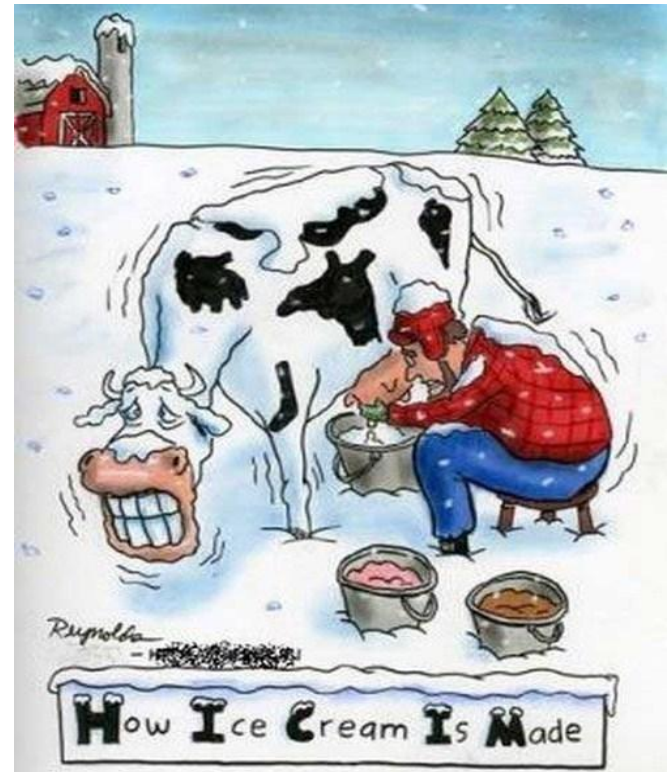


**Reduced Doses
Increased Frequency
Monitoring for Toxicity and Efficacy**



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

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

Paralytics (pro/con)

Pros

- ✔ Effective
- ✔ Does not cause hypotension
- ✔ Leads to more rapid cooling

Cons

- ✔ Masks insufficient sedation
- ✔ Masks seizure activity
- ✔ Polyneuromyopathy in prolonged paralysis

Paralytics Used in Hypothermia

Medication	Onset	Duration of Action (DOA)	Comments
Vecuronium	180 sec	33 min	<ul style="list-style-type: none">• Metabolized by P450 enzymes• 3-fold increase in DOA with hypothermia
Rocuronium	75 sec	33 min	<ul style="list-style-type: none">• Primarily eliminated in bile• 2-fold decrease in systemic clearance
Atracurium	110 sec	43 min	<ul style="list-style-type: none">• 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 $>30^{\circ}\text{C}$
- ◆ Management of arrhythmias
 - ◆ Fluid balance
 - ◆ Electrolyte balance (Magnesium and Potassium)
 - ◆ Less responsive to anti-arrhythmics



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

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



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

