Pharmacologic Options for Reducing the Shivering Response to Therapeutic Hypothermia

Kyle A. Weant et al.

Pharmacotherapy 2010;30(8):830–841.

2010/08/09

Reporter: R2徐英洲

Supervisor : VS王瑞芳

Introduction1

- Cerebral ischemia occurs when there is inadequate blood flow to the brain for more than 5 minutes.
- As core temperature increases by 0.5˚C or more above 37˚C, postischemic damage is increased.

Introduction2

- Elevated temperatures have also been shown to correlate with
  - the formation of free radicals and the release of glutamate into the extracellular space during times of ischemia.
  - Activation of *N*-methyl-D-aspartate (NMDA) receptors, which increases intracellular calcium levels and enhances the detrimental effects of free radicals generated by the release of arachidonic acid

→ triggers a chronic inflammatory response

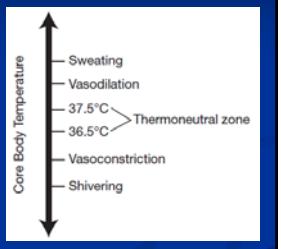
→ leading to a slow progressive neurodegeneration.

Introduction3

- each 1˚C decrease in body temperature, the cerebral metabolic rate decreases by 6–7%
- Therapeutic hypothermia works by
  - Retarding destructive enzymatic reactions
  - suppressing free radical reactions
  - protecting the fluidity of lipoprotein membranes
  - reducing the oxygen demand in low-flow regions
  - reducing intracellular acidosis
  - inhibiting the biosynthesis, release, and uptake of excitatory neurotransmitters.

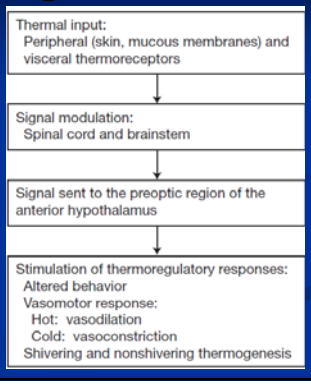
Thermoregulation1

- In humans, core temperature is normally maintained within a tight range (36.5–37.5˚C) known as the interthreshold range or thermoneutral zone



Thermoregulation2

- Thermoregulatory control involves the interplay between
  - peripheral and central thermoreceptors
  - an integrating control center (hypothalamus)
  - efferent autonomic and behavioral response systems



Thermoregulation3

- For successful induction and maintenance of therapeutic hypothermia, thermoregulatory responses must be overcome.
- Over the years, various agents have been used in the **operating room** to control intra- and postoperative shivering.

Thermoregulation4

- General anesthesia can greatly impair normal control of body temperature, affecting both warm and cold thermoregulatory responses, increasing the interthreshold range from approximately 0.4°C to 4.0°C.
- volatile and nonvolatile anesthetics appear to have vastly different effects on norepinephrine activity and potentially adipocytes, thus impacting shivering response.

Thermoregulation5

- Thus, we evaluated the available data regarding various pharmacologic agents used in the inhibition of shivering in the **absence of general anesthesia**.

Thermoregulation6

- A PubMed search (1966–March 2009) was conducted to identify all human investigations published in English that discussed pharmacologic mechanisms for the control of shivering.
- No studies that specifically evaluated the control of shivering in nonsurgical patients; therefore, the studies included in this review were all conducted **in healthy volunteers**.

Table 2. Drugs Studied for Altering the Shivering Response

Drug	Proposed Mechanism
Ondansetron[36]	5-HT antagonism
Tramadol[37]	Inhibition of norepinephrine uptake, 5-HT uptake, facilitation of 5-HT release, activation of μ-opioid receptors
Magnesium[38, 39]	NMDA antagonist, calcium antagonist
Clonidine[40, 41]	α_2-Agonist
Dexmedetomidine[42]	α_2-Agonist
Meperidine[43]	Decrease in ACTH, cortisol, growth hormone oxygen consumption, catecholamine excretion
Nalbuphine[44]	Mixed agonist-antagonist opioid, decrease in ACTH, cortisol, growth hormone oxygen consumption, catecolamine excretion
Buspirone[46]	5-HT_{1A} partial agonist
Dantrolene[47]	Inhibition of excitation-contraction coupling skeletal muscles, calcium release
Propofol[48]	Sedative, suppression of excitatory neurotransmitters
Doxapram[49]	Stimulates dopamine release from carotid bodies

5-HT = serotonin; NMDA = *N*-methyl-D-aspartate; CNS = central nervous system; ACT

Drug	Adverse Effects
Ondansetron[36]	Elevated liver enzyme levels, cardiac dysrhythmias
Tramadol[37]	Dyspnea, dizziness, somnolence, seizures, flushing
Magnesium[38, 39]	Hypotension, heart block, CNS depression, hyporeflexia, respiratory tract paralysis
Clonidine[40, 41]	Dizziness, sedation, somnolence
Dexmedetomidine	Nausea, cardiac dysrhythmias, hypotension
Meperidine[43]	Dizziness, somnolence, seizures, hypotensio
Nalbuphine[44]	Dizziness, somnolence, sweating, immune hypersensitivity reaction
Buspirone[46]	Sedation, nausea, dizziness
Dantrolene[47]	Dizziness, constipation, diplopia, fatigue, hepatotoxicity
Propofol[48]	Bradyarrhythmia, hypotension, propofol infusion syndrome
Doxapram[49]	Cardiac dysrhythmia, dyspnea

Serotonin1

- it was proposed that the balance of norepinephrine and 5-HT in the preoptic-anterior hypothalamus controls the body temperature set point.
- When given alone in the **rat model**, 5-HT3 antagonists have been shown to induce Hypothermia .

Serotonin2

- **Volunteers** were administered ondansetron, a 5-HT3 antagonist, or placebo.

Drug and Dose, No. of Patients	Cooling Method	Shivering Temperature (°C)
Ondansetron ~50 mg	Forced air	36.3 (p=0.76)
Placebo (n=10)[36]		36.3

Adverse Effects	Other Outcomes
None	None

→ the use of ondansetron alone may not be effective in the facilitation of therapeutic hypothermia.

Serotonin3

- Ondansetron has been used to manage postoperative shivering with some efficacy but did not reduce the shivering threshold.
  -->may be most useful for inhibiting nonthermoregulatory shivering.

Tramadol

- This study did demonstrate tramadol's predicted ability to reduce the vasoconstrictive and shivering thresholds, but the impact was modest (0.5 and 0.2°C, respectively).

Tramadol 125 mg	Circulating water, forced air	35.3
Tramadol 250 mg		35.0
Tramadol 250 mg + naloxone 1.1 mg		35.6
Placebo (n=8)[37]		35.9

Not reported	Interthreshold range nearly doubled; naloxone returned shivering threshold to near control levels

Magnesium (NMDA antagonist)1

- The NMDA receptors may help to modulate noradrenergic and serotonergic neurons in the locus coeruleus and provide some measure of thermoregulation.
- Magnesium bolus doses and infusions have been used to reduce both pain and paralytic requirements during **anesthesia induction**.

Magnesium (NMDA antagonist)2

- The main limitation of this investigation was the lack of a control group; thus, the results are largely dependent on multiple linear regression to determine variations in response.

Meperidine 50–100 mg Meperidine + buspirone 30–60 mg Meperidine + ondansetron 8–16 mg Meperidine + ondansetron + magnesium 4–6 g (n=22)[38]	Circulating water	Not reported

Vasodilation 88% vs 29% (magnesium group vs all other groups, p=0.024) No significant change in blood pressure	Magnesium group: higher comfort scores (p<0.001) and reduced time to achieve target temperature (p=0.039)

Magnesium (NMDA antagonist)3

- Magnesium was shown to decrease time to target temperature and increase patient comfort.
- This was likely due to its vasodilatory properties that counteract the normal adaptive response to surface cooling of vasoconstriction.

Magnesium (NMDA antagonist)4

- the results were not clinically impressive with regard to impact on the shivering threshold.
- The study also demonstrated how postoperative antishivering interventions **may not** be applicable to the out-of-hospital setting, as magnesium's impressive antishivering efficacy was demonstrated in the surgical arena.

Magnesium 80 mg/kg + continuous infusion	Cool Ringer's lactate infusion	36.3 (p=0.04)
Control (n=9)[30]		36.6

Tachycardia (p=0.03)	Thermal comfort increased (p=0.019); no difference in gain of shivering response (p=0.344)

α 2-agonists1

- This study demonstrated a statistically, and potentially clinically, significant decrease in vasoconstriction and shivering thresholds (1.2°C and 1.6°C, respectively).
- Clonidine significantly affected heart rate and blood pressure. This may limit the use of this therapy.

Clonidine 3 μg/kg p.o. Clonidine 6 μg/kg p.o. Clonidine 9 μg/kg p.o. Placebo (n=6)[40]	Water immersion

30.35 (p<0.05) 29.48 (p<0.05) 29.32 (p<0.05) 31.52	Bradycardia and hypotension (p<0.05) Sedation in 6–9-μg/kg groups

α 2-agonists2

- Although the treatment group experienced a lowering of their shivering threshold, the effect is likely not clinically significant (0.5°C).
- This may be in part due to the use of a lower dose than that used in the previous study.

Clonidine 75 μg i.v. Placebo (n=7)[41]	Cool saline	35.4 (p<0.05) 35.9

Not reported	Decreased oxygen consumption during shivering in clonidine group (p<0.05); as-needed boluses stopped shivering in all but one volunteer

α 2-agonists3

- This study demonstrated the efficacy of dexmedetomidine, as well as the possible mechanism.
- theimpact of high-dose dexmedetomidine in lowering the shivering threshold was **greater** than that of clonidine (2.4°C vs 1.6°C), but this may be a function of the high serum concentration used in the study.

Dexmedetomidine to target concentration: 0.3 ng/ml 0.6 ng/ml Placebo (n=9)[42]	Forced air, circulating water	 34.7 (p=0.05) 34.0 (p=0.05) 36.0

Bradycardia and hypotension (p<0.05) Sedation	Decreased catecholamine use (p<0.05)

Opioids1

- The apparent impact on the shivering threshold of 1.7°C was impressive.
- However, the effect of meperidine was difficult to discern from that of **skin warming**, which has been shown to lower thermoregulatory thresholds in some studies.

Meperidine 9 μg/ml Skin warming Meperidine + warming Control (n=8)[43]	Forced air, warming blanket	34.2 (p<0.01) 34.9 (p=0.01) 33.8 (p<0.01)

Sedation	Meperidine + skin warming decreased vasoconstriction by 0.9°C (p<0.01)

Opioids2

- The study sought primarily to more precisely define the actions of meperidine on lowering the shivering threshold and the exact receptors responsible for its efficacy.(κ receptor or anticholinergic ?)
- The fact that atropine raised the shivering threshold demonstrates that anticholinergic effects are most assuredly not the mechanism.

Nalbuphine 0.2 µg/ml	Forced air, circulating water	34.8 (p<0.05)
Nalbuphine 0.4 µg/ml		34.4 (p<0.05)
Atropine 1 mg		36.2 (p<0.05)
Placebo (n=8)[44]		35.5
Atropine increased heart rate and shivering by 2.8°C/µg/ml	Decreased vasoconstriction by 2.6°C/µg/ml	

Combination Therapy1

- The combination of meperidine with dexmedetomidine seems to support the notion that the activity of meperidine in this setting is mediated **through the α2-receptor** rather than the opioid receptor.
- The meperidine dose used in this study was about half of that used in the previous study, leaving open the question of what the target serum concentration should really be.

Meperidine 0.3 µg/ml	Circulating water, cool Ringer's lactate solution	35.5 (p<0.001)
Dexmedetomidine 0.4 ng/ml		36.0 (p<0.001)
Meperidine + dexmedetomidine		34.7 (p<0.001)
Control (n=10)[45]		36.7
Combination therapy increased risk of sedation	No significant difference in heart rate or mean arterial pressure	

Combination Therapy2

- the use of buspirone in this setting may provide for a combined dose-sparing effect and lessen the occurrence of adverse effects.

Buspirone 60 mg	Circulating water, forced air, cool Ringer's lactate solution	35.0 (p<0.05)
Meperidine 8 µg/ml		33.4 (p<0.05)
Buspirone 30 mg + meperidine 4 µg/ml		33.4 (p<0.05)
Control (n=8)[46]		35.7
Sedation Respiratory difficulty	No significant difference in heart rate or mean arterial pressure	

Dantrolene

- Although dantrolene demonstrated efficacy in lowering the shivering threshold in both of these study groups the effect was only modest (0.3°C and 0.4°C) and therefore not likely to be clinically relevant.
- Dantrolene use reduced the shivering gain, likely due to the peripheral skeletal muscle activity of the drug, which would reduce thermogenesis.

Dantrolene 2.5 mg/kg + continuous infusion	Forced air, circulating water, cool Ringer's lactate solution	36.3 (p=0.01)
Control (n=9)[47]		36.7
Not reported	Reduced oxygen consumption by 39% from shivering (p=0.02)	

Propofol

- This study demonstrated a profound lowering of the shivering threshold in these patients; however, the study is **limited** by its small sample size and the fact that all subjects were male.
- Patients with hypotension after cardiac arrest may not tolerate propofol at relatively high doses.

Propofol 2 µg/ml	Circulating water Forced air	34.4 (p<0.05)[b]	Mean arterial pressure decreased
Propofol 4 µg/ml		33.6	
Propofol 8 µg/ml		31.5	
Control (n=5)[48]		35.6	

Doxapram

- Both animal and human models have demonstrated its usefulness in the treatment of postanesthetic shivering.
- Information regarding how the patients were warmed and cooled was not provided, which is a major limitation of the research.
- Perhaps this agent may be more functional in combination with another moderately effective agent or to help maintain lower doses of possibly toxic agents like meperidine.

Doxapram 4 µg/ml	Not reported	35.7 (p=0.01)
Placebo (n=9)[49]		36.2
Not reported	No impact on vasoconstriction thresholds	

Comparison and Limitations1

- Interpretation of these data is complicated by the various techniques used for induction of hypothermia and lack of comparative studies.
- it is difficult to fully predict how oral drugs will perform during an acute clinical event; oral absorption could be **compromised** from impairment of gastrointestinal peristalsis and reduced organ perfusion and congestion of the venous system.

Comparison and Limitations2

- All the studies were in **healthy volunteers**, which, although more relevant than the anesthetized patient, **do not** represent the actual patient population that would be receiving this therapy.

Comparison and Limitations3

- Identification of shivering activity is often based on a clinical diagnosis.
- Because shivering often begins in small muscles, the timing of the diagnosis is often delayed.
- The observation is dependent on intense monitoring, which in a **busy** emergency department with limited resources provides a challenge.
- It is also difficult to discern shivering from possible seizure activity.

Future Research

- Future investigations should evaluate the efficacy of the various therapies in the **target population** (patients requiring therapeutic hypothermia) as well as their safety, as adverse effects.
- Interventions should be standardized across trials to allow for comparative analysis and to enhance isolation of true pharmacologic effects.

Conclusion1

- Several pharmacologic treatments have been used, either alone or in combination, that safely and effectively prevent or treat shivering after the induction of hypothermia in patients **undergoing surgery**.
- Although we found **no studies** that address antishivering therapy in this patient population, many studies evaluating various agents in **healthy volunteers** have attempted to lay the groundwork for possible therapies.

Conclusion2

- clonidine, dexmedetomidine, and meperidine have demonstrated the greatest and most clinically relevant impact on depression of the shivering threshold.
- Further studies should evaluate additional agents, standardize physical interventions, and monitor for adverse effects of the drugs.

Thanks for your attention !