

Pharmacologic Options for Reducing the Shivering Response to Therapeutic Hypothermia

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Recent literature has demonstrated significant improvements in neurologic outcomes in patients who have received induced hypothermia in the setting of out-of-hospital cardiac arrest. Through multiple metabolic mechanisms, the induction of hypothermia slows the progression and devastation of transient cerebral hypoxia. Despite these benefits, the desired reduction in core temperature is often a challenging venture as the body attempts to maintain homeostasis through the induction of thermoregulatory processes aimed at elevating body temperature. Shivering is an involuntary muscular activity that enhances heat production in an attempt to restore homeostasis. For successful induction and maintenance of induced hypothermia, shivering, as well as other thermoregulatory responses, must be overcome. Several pharmacologic options are available, either used alone or in combination, that safely and effectively prevent or treat shivering after the induction of hypothermia. We conducted a PubMed search (1966–March 2009) to identify all human investigations published in English that discussed pharmacologic mechanisms for the control of shivering. Among these options, clonidine, dexmedetomidine, and meperidine have demonstrated the greatest and most clinically relevant impact on depression of the shivering threshold. More research in this area is needed, however, and the role of the clinical pharmacist in the development and implementation of this therapy needs to be defined.

Key Words: hypothermia, shivering, doxapram, propofol, opioids, dantrolene, neuromuscular blocking agents, α_2 -agonists, serotonin.
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Interest in therapeutic hypothermia for a variety of acute ischemic situations has increased dramatically over the past several years.¹ Although used routinely in conjunction with anesthesia in the operating room since the 1950s, its permutation into other venues had remained somewhat limited.² In 2002, however, results from two randomized controlled trials that evaluated the use of mild-to-moderate hypothermia (32–34°C)

in the setting of out-of-hospital cardiac arrest when the initial rhythm was ventricular fibrillation or nonperfusing ventricular tachycardia were published.^{3, 4} The data led the Advanced Life Support Task Force of the International Liaison Committee of Resuscitation to recommend therapeutic hypothermia in unconscious adults with spontaneous circulation after out-of-hospital cardiac arrest when the initial rhythm was ventricular fibrillation.⁵

Cerebral ischemia occurs when there is inadequate blood flow to the brain for more than 5 minutes and results in a multitude of reactions.^{6, 7} Of interest, body temperature can have a profound impact on these deleterious processes. As core temperature increases by 0.5°C or more above 37°C, postischemic damage is increased.⁸⁻¹⁰ 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.^{11, 12} Hyperthermia activates *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.¹¹ This initial neuronal damage after ischemia and reperfusion injury triggers a chronic inflammatory response involving microglia-derived mediators, becoming a vicious cycle leading to a slow progressive neurodegeneration.¹²

Hypothermia, however, appears to have an effect directly contrary to that of hyperthermia. For each 1°C decrease in body temperature, the cerebral metabolic rate decreases by 6–7%.¹³ 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, and inhibiting the biosynthesis, release, and uptake of excitatory neurotransmitters.^{14, 15} Induced therapeutic hypothermia allows tissues to endure anoxic no-flow states and improves oxygen supply to areas of ischemic brain, as well as decreases intracranial pressure.¹⁶⁻¹⁹ It also decreases the concentrations of excitatory amino acids and lactate during ischemia and reperfusion injury.^{7, 17, 20-22}

Thermoregulation

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

neutral zone (Figure 1).²³ Thermoregulatory control involves the interplay between peripheral and central thermoreceptors, an integrating control center (hypothalamus), and efferent autonomic and behavioral response systems (Figure 2).²⁴ Mean skin temperature represents approximately 20% of total thermoregulatory input.²⁵⁻²⁷ Heat balance is typically regulated by means of vasomotor responses. Shivering, which increases heat production 2–5-fold, is activated when behavioral compensations and maximal vasoconstriction are insufficient to maintain core temperature.^{28, 29}

Shivering is an involuntary muscular activity that enhances heat production in an attempt to restore homeostasis.^{26, 30} Available data suggest that the shivering threshold is 1°C lower than the vasoconstriction threshold.³¹ When the shivering threshold is reached, motor neurons are recruited in sequence and with increasing size, as hypothermia persists.²⁶ The end result of this autoregulatory process is a response that increases heat production up to 600% and triples oxygen consumption.^{29, 32} However, these responses are not as effective over extended periods as they are in the short-term. This increase in metabolic activity is not sustainable and reduces to an approximate doubling of the baseline rate over time.³³ Similarly, the overall heat generation gain is far less effective than the initial vasoconstrictive

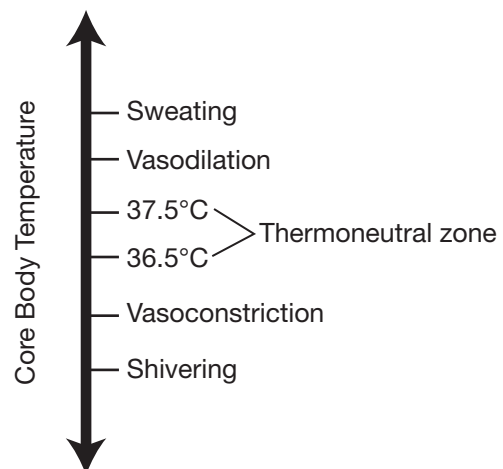


Figure 1. The process of thermoregulation. In humans, core temperature is normally maintained within a tight range (36.5–37.5°C) known as the interthreshold range or thermoneutral zone. When core temperatures fall below this range, thermoregulatory responses such as vasoconstriction and shivering are triggered. When temperatures rise above this range, vasodilation and sweating are typical homeostatic responses.

response of the body, as much of the heat generated from skeletal muscle contraction will be lost to the environment rather than retained in the core; therefore, core temperature will increase only about 1°C.

For successful induction and maintenance of therapeutic hypothermia, thermoregulatory responses must be overcome. Certain pharmacologic agents widen the interthreshold range by lowering the vasoconstriction and shivering thresholds and/or raising the vasodilation and sweating thresholds.^{23, 34} Over the years, various agents, such as opioids, α_2 -agonists, selective serotonin (5-HT) reuptake inhibitors, 5-HT agonists or antagonists, cholinomimetics, NMDA antagonists, methylphenidate, urapidil, and dantrolene, have been used in the operating room to control intra- and postoperative shivering.²³

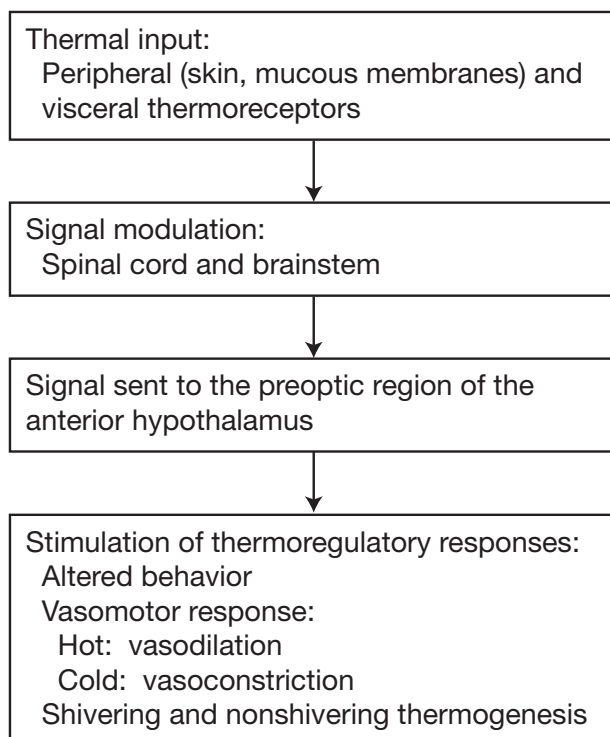


Figure 2. Thermoregulatory control involves the interplay between peripheral and central thermoreceptors, an integrating control center (hypothalamus), and efferent autonomic and behavioral response systems. Thermoregulatory inputs are modulated in the spinal cord and brainstem and integrated within the preoptic region of the anterior hypothalamus. When the feedback from skin and core thermoreceptors deviates from the reference temperature in the preoptic area, a thermoregulatory response is generated. Thermoregulatory responses include altered behavior, vasomotor response (vasodilation and sweating in response to heat, and vasoconstriction and piloerection in response to cold), and shivering and nonshivering thermogenesis.

The challenge in using these drugs in the therapeutic hypothermia arena, however, is that their success or failure is influenced by the general anesthesia received by the patient. 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.³⁵ In addition, volatile and nonvolatile anesthetics appear to have vastly different effects on norepinephrine activity and potentially adipocytes, thus impacting shivering response.²³ As such, uniform application of postanesthesia antishivering therapy recommendations to the setting of out-of-hospital cardiac arrest cannot be recommended at this time. Thus, we evaluated the available data regarding various pharmacologic agents used in the inhibition of shivering in the absence of general anesthesia.

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. Search terms were 5-HT agonists and antagonists, propofol, 5-HT reuptake inhibitors, α_2 -agonists, opioids, NMDA antagonists, cholinomimetics, urapidil, dexamethasone, dantrolene, and shivering. To adequately discern efficacy in shivering response not due to the receipt of anesthetics, we limited our search to studies that were full reports of any pharmacologic antishivering intervention in nonsurgical patients. Data on nonpharmacologic interventions, case reports, and case series were excluded. We found 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. Agents included ondansetron, tramadol, magnesium, clonidine, dexmedetomidine, meperidine, nalbuphine, buspirone, dantrolene, propofol, and doxapram (Table 1).^{36–49} These agents have various mechanisms of action and the potential for adverse effects (Table 2).^{36–44, 46–49}

Pharmacologic Therapies

Serotonin Manipulation

In 1963, it was proposed that the balance of norepinephrine and 5-HT in the preoptic-anterior hypothalamus controls the body temperature set point.⁵⁰ Intracerebroventricular injection of 5-HT in animal models induced a shivering and vasoconstrictive response, whereas injection of norepinephrine and epinephrine lowered normal resting temperature.⁵¹ Of

Table 1. Studies of Pharmacologic Options for Reducing the Shivering Response in Healthy Volunteers

Drug and Dose, No. of Patients	Cooling Method	Shivering Temperature (°C)	Adverse Effects	Other Outcomes
Ondansetron ~50 mg Placebo (n=10) ³⁶	Forced air	36.3 (p=0.76) 36.3	None	None
Tramadol 125 mg Tramadol 250 mg Tramadol 250 mg + naloxone 1.1 mg Placebo (n=8) ³⁷	Circulating water, forced air	35.3 35.0 35.6 35.9	Not reported	Interthreshold range nearly doubled; naloxone returned shivering threshold to near control levels
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 80 mg/kg + continuous infusion Control (n=9) ³⁹	Cool Ringer's lactate infusion	36.3 (p=0.04) 36.6	Tachycardia (p=0.03)	Thermal comfort increased (p=0.019); no difference in gain of shivering response (p=0.344)
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	
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
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)
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)
Nalbuphine 0.2 µg/ml Nalbuphine 0.4 µg/ml Atropine 1 mg Placebo (n=8) ⁴⁴	Forced air, circulating water	34.8 (p<0.05) 34.4 (p<0.05) 36.2 (p<0.05) 35.5	Atropine increased heart rate and shivering by 2.8°C/µg/ml Atropine increased vasoconstriction and shivering thresholds	Decreased vasoconstriction by 2.6°C/µg/ml
Meperidine 0.3 µg/ml Dexmedetomidine 0.4 ng/ml Meperidine + dexmedetomidine Control (n=10) ⁴⁵	Circulating water, cool Ringer's lactate solution	35.5 (p<0.001) 36.0 (p<0.001) 34.7 (p<0.001) 36.7	Combination therapy increased risk of sedation	No significant difference in heart rate or mean arterial pressure

Table 1. Studies of Pharmacologic Options for Reducing the Shivering Response in Healthy Volunteers (continued)

Drug and Dose, No. of Patients	Cooling Method	Shivering Temperature (°C)	Adverse Effects	Other Outcomes
Buspirone 60 mg Meperidine 8 µg/ml	Circulating water, forced air, cool	35.0 (p<0.05) 33.4 (p<0.05)	Sedation Respiratory difficulty	No significant difference in heart rate or mean arterial pressure
Buspirone 30 mg + meperidine 4 µg/ml	Ringer's lactate solution	33.4 (p<0.05)		
Control (n=8) ⁴⁶		35.7		
Dantrolene 2.5 mg/kg + continuous infusion	Forced air, circulating water,	36.3 (p=0.01)	Not reported	Reduced oxygen consumption by 39% from shivering (p=0.02)
Control (n=9) ⁴⁷	cool Ringer's lactate solution	36.7		
Propofol 2 µg/ml	Circulating water	34.4 (p<0.05) ^b		Mean arterial pressure decreased
Propofol 4 µg/ml	Forced air	33.6		
Propofol 8 µg/ml		31.5		
Control (n=5) ⁴⁸		35.6		
Doxapram 4 µg/ml	Not reported	35.7 (p=0.01)	Not reported	No impact on vasoconstriction thresholds
Placebo (n=9) ⁴⁹		36.2		

^aAll studies were randomized, crossover design.

^bFor trend.

interest, 5-HT appears to have various effects depending on the site of action within the hypothalamus: when injected into the preoptic area, it appears to evoke hypothermia; in the rostral hypothalamus, it results in hyperthermia; and in the midbrain, it appears to inhibit both portions of temperature control.^{52, 53} This suggests that 5-HT plays an important role in the finely tuned homeostasis of temperature regulation at the hypothalamic level.

The role of specific 5-HT subtypes in temperature is somewhat debatable. There is evidence that a 5-HT₃ agonist can induce hyperthermia, which can subsequently be terminated by a receptor antagonist.⁵⁴ In addition, when given alone in the rat model, 5-HT₃ antagonists have been shown to induce hypothermia.⁵⁵ To test this concept, volunteers were administered ondansetron, a 5-HT₃ antagonist, or placebo (Table 1).³⁶ The results demonstrated that the use of ondansetron alone may not be effective in the facilitation of therapeutic hypothermia. The dose used (mean 49 mg) was based on the dosing for chemotherapy-induced nausea and vomiting, and was far in excess of what a typical dose would be for this agent in this setting. Of interest, ondansetron has been used to manage postoperative shivering with some efficacy but did not reduce the shivering threshold.⁵⁶ Thus, 5-HT₃ antagonists

may be most useful for inhibiting nonthermoregulatory shivering.

To evaluate tramadol's possible role in altering thermogenic homeostatic mechanisms, a study was designed to investigate its effect in eight volunteers on 4 study days (Table 1).³⁷ 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). Of interest, naloxone only partially reversed the actions of tramadol on thermoregulation and predominantly on the shivering spectrum. Therefore, perhaps the µ-opioid activity of tramadol contributes only a small portion to the drug's overall activity in this setting. Also, a dose-response relationship was reported; therefore, the modest impact on shivering thresholds may be augmented with higher tramadol plasma concentrations, as an impressive 4.2°C/µg/ml decrease was reported by the authors. No clinically significant sedative effects were documented during this study.

N-Methyl-D-Aspartate Antagonists

The NMDA receptors may help to modulate noradrenergic and serotonergic neurons in the locus coeruleus and provide some measure of thermoregulation.²³ Magnesium bolus doses and infusions have been used to reduce both pain and

Table 2. Drugs Studied for Altering the Shivering Response

Drug	Proposed Mechanism	Adverse Effects
Ondansetron ³⁶	5-HT antagonism	Elevated liver enzyme levels, cardiac dysrhythmias
Tramadol ³⁷	Inhibition of norepinephrine uptake, 5-HT uptake, facilitation of 5-HT release, activation of μ -opioid receptors	Dyspnea, dizziness, somnolence, seizures, flushing
Magnesium ^{38, 39}	NMDA antagonist, calcium antagonist	Hypotension, heart block, CNS depression, hyporeflexia, respiratory tract paralysis
Clonidine ^{40, 41}	α_2 -Agonist	Dizziness, sedation, somnolence
Dexmedetomidine ⁴²	α_2 -Agonist	Nausea, cardiac dysrhythmias, hypotension
Meperidine ⁴³	Decrease in ACTH, cortisol, growth hormone oxygen consumption, catecholamine excretion	Dizziness, somnolence, seizures, hypotension
Nalbuphine ⁴⁴	Mixed agonist-antagonist opioid, decrease in ACTH, cortisol, growth hormone oxygen consumption, catecholamine excretion	Dizziness, somnolence, sweating, immune hypersensitivity reaction
Buspirone ⁴⁶	5-HT _{1A} partial agonist	Sedation, nausea, dizziness
Dantrolene ⁴⁷	Inhibition of excitation-contraction coupling skeletal muscles, calcium release	Dizziness, constipation, diplopia, fatigue, hepatotoxicity
Propofol ⁴⁸	Sedative, suppression of excitatory neurotransmitters	Bradycardia, hypotension, propofol infusion syndrome
Doxapram ⁴⁹	Stimulates dopamine release from carotid bodies	Cardiac dysrhythmia, dyspnea

5-HT = serotonin; NMDA = *N*-methyl-D-aspartate; CNS = central nervous system; ACTH = adrenocorticotropic hormone.

paralytic requirements during anesthesia induction.⁵⁷ In addition, magnesium was effective in the termination of postanesthetic shivering.⁵⁸ A benefit of magnesium is the additional possibility for neuroprotection. The agent's impact on smooth muscle tone may induce cerebral vasodilation and has provided some benefit in animal models.^{59, 60}

To evaluate the possible role of magnesium in the initiation of therapeutic hypothermia, 22 volunteers were randomly assigned to one of four therapies: meperidine monotherapy; meperidine plus buspirone; meperidine plus ondansetron; or meperidine, ondansetron, and magnesium sulfate (Table 1).³⁸ This well-designed study investigated multiple variables in the pharmacologic management of subjects during induced hypothermia. 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. 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. Although the presence of shivering was recorded in this investigation, these data were not reported. However, the significant impact of magnesium on subject

comfort throughout the study suggests that magnesium was beneficial in this outcome.

In another investigation, the effect of a magnesium infusion on the threshold and gain of shivering was evaluated (Table 1).³⁹ Although intriguing, the results were not clinically impressive with regard to impact on the shivering threshold. This study was distinctive in that it used a continuous infusion of magnesium, as well as invasive cooling techniques. Despite not being an end point of the investigation, no significant difference was noted in cooling rate ($p=0.501$). Magnesium's benefit in the previous study³⁸ on the rate of cooling was likely related to its vasodilatory properties, and thus the agent may be more effective with surface cooling techniques than with the invasive techniques used in this study. 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. This may be because after anesthesia, a patient's core temperature is only slightly below the normal shivering threshold, yet homeostatic mechanisms are impaired secondary to anesthetic therapy. Therefore, minor shivering threshold changes in that population may result in larger clinical implications.⁴²

α_2 -Agonists

The α_2 -adrenergic receptors are G_i - G_o protein-coupled receptors, which are not only expressed in the brain and spinal cord but are also present at sympathetic nerve terminals and in different peripheral organs.⁶¹ These receptors are targets for multiple endogenous catecholamines and pharmacologic agents.⁶² Three subtypes of α_2 -adrenergic receptors with different pharmacologic profiles and divergent tissue-distribution patterns have been characterized. However, the subtype of general clinical importance is the α_{2A} -adrenergic receptor. Stimulation of this receptor is responsible for most of the classic effects of α_2 -agonists, including hypotension, sedation, and analgesia. The α_{2B} -adrenergic receptor is responsible for the transient hypertensive phase after systemic injection of α_2 -agonists and is likely involved in the analgesic effects constitutive to their intrathecal administration. Agonists and antagonists of the α_2 receptor have been available to clinicians for several decades, but none of the compounds so far exhibits subtype selectivity. The primary use of α_2 -agonists has long been the treatment of hypertension. However, animal models have shown that dexmedetomidine, an α_2 -adrenergic agonist similar to clonidine, causes profound hypothermia in controls, but this effect is completely abolished in those lacking the α_{2A} -adrenergic receptor subtype.⁶² Many human studies have extended this research and demonstrated the efficacy of both clonidine and dexmedetomidine in the setting of postoperative shivering; it naturally follows that these agents may have a role in altering thermoregulatory shivering.⁶³⁻⁶⁶

To evaluate the impact of clonidine in the nonanesthetic area, three different doses of clonidine were investigated in six healthy human subjects (Table 1).⁴⁰ This study demonstrated a statistically, and potentially clinically, significant decrease in vasoconstriction and shivering thresholds (1.2°C and 1.6°C, respectively). This effect also appeared to be dose dependent, implying that the drug could be titrated based on individual response. As reported in this study, however, clonidine significantly affected heart rate and blood pressure. This may limit the use of this therapy, as therapeutic hypothermia can induce cardiovascular complications including bradycardia and possibly hypotension.⁶⁷ Of interest, no effect was noted on the sweating threshold; however, the interthreshold range increased in a dose-dependent manner. Although

the reasons behind this are not entirely clear, it is likely related to the density of α_2 -adrenergic receptors in the hypothalamus.⁶⁸

Another group of investigators attempted to determine the thermoregulatory impact of clonidine in a similar fashion in seven healthy volunteers (Table 1).⁴¹ In this study, investigators used intravenous clonidine at a non-weight-based dose, and they allowed its use on an as-needed basis in addition to before hypothermia induction. 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.⁴⁰ The observed efficacy of subsequent clonidine doses at terminating shivering activity appears to support this. This may also be secondary to the use of a different formulation of clonidine, although available data suggest that the onset of response and peak response should be similar between the two formulations.⁶⁹ The most important results of this study were that clonidine could terminate shivering and decrease systemic oxygen consumption during shivering.⁴¹ However, a thorough evaluation of the latter is somewhat limited because actual numbers are not presented regarding this outcome.

Another study attempted to determine if dexmedetomidine could produce similar results to those of clonidine (Table 1).⁴² This study demonstrated the efficacy of dexmedetomidine, as well as the possible mechanism. Although this study sought to target serum drug concentrations of 0.3 and 0.6 ng/ml, the actual concentrations achieved were 0.4 and 0.8 ng/ml. The authors also documented clinically significant sedation with both doses, although the proportion of patients experiencing sedation was not quantified. The authors did document a dose-dependent alteration in thermoregulatory thresholds but not with hemodynamic or catecholamine parameters, possibly suggesting different mechanisms of action. These results were somewhat consistent with those of the previous study,⁴¹ providing a modicum of confirmation. Of interest, the impact 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 (0.8 ng/ml).

Opioids

Morphine sulfate has become an integral part

of therapy for critically ill patients and is used to facilitate mechanical ventilation and control pain.⁷⁰ Meperidine, in contrast to other opioids, possesses additional antishivering action at equianalgesic doses and inhibits shivering twice as much as vasoconstriction. However, when meperidine is used as a single drug, large plasma concentrations are needed to reduce the shivering threshold to below 34°C. Various opioids, including meperidine, morphine, and nalbuphine (a mixed agonist-antagonist opioid), have been used in the surgical realm for the treatment of postanesthetic shivering with varying levels of efficacy.⁷⁰⁻⁷³

One group of investigators set out to determine if the benefits noted in the operating room could be extrapolated to other areas of care (Table 1).⁴³ The apparent impact on the shivering threshold of 1.7°C was impressive when compared with the other therapies discussed so far. 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.^{25, 74} The challenge with these results is the functional implementation of such an approach. Most current protocols and devices used to induce therapeutic hypothermia involve the use of surface cooling; this would be quite a change and demonstrates that this current practice may be more of a hindrance than helpful.

To test if meperidine's efficacy in lowering the shivering threshold is tied to its κ -receptor activity or its possible central anticholinergic activity, a prospective, double-blind, randomized study evaluated the value of nalbuphine and atropine compared with placebo for inhibiting shivering (Table 1).⁴⁴ 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. The fact that nalbuphine reduced both vasoconstriction and shivering thresholds comparably implies that κ activity is not the primary mechanism by which meperidine exerts its effect. The fact that atropine raised the shivering threshold demonstrates that anticholinergic effects are most assuredly not the mechanism. However, the authors discovered that nalbuphine reduced the shivering threshold by 1.1°C in the high-dose group, but this was only to 34.4°C, above that which would be targeted in this setting. The concomitant reduction in the sweating threshold may have further implications for rewarming of the patient because vasoconstriction normally decreases cutaneous heat loss and facilitates core rewarming.

Combination Therapy

Another study sought to evaluate the additive impact of various therapies to gain more clinically effective lowering in the shivering threshold (Table 1).⁴⁵ This study provides some interesting insight into not only possible therapies but also potential mechanisms involved in the shivering response. The combination of meperidine with dexmedetomidine seems to support the notion that the activity of meperidine in this setting is mediated through the α_2 -receptor rather than the opioid receptor.⁷⁵ Although the observed decrease in shivering threshold was impressive (2°C), it was only reduced to 34.7°C, above that which is typically targeted in therapeutic hypothermia. The meperidine dose used in this study was about half of that used in the previous study,⁴⁴ leaving open the question of what the target serum concentration should really be. Also, this study stimulated vasoconstriction in patients before inducing core hypothermia, and no data are available on the impact of the various therapies on this end point. If the novel therapy of skin warming had been used (vs surface cooling), the result may have been more dramatic. Skin temperature contributes 20% to control of vasoconstriction and shivering; therefore, when added to the 2°C difference seen in this study, the shivering threshold may fall below 34°C and achieve recommended hypothermia targets.^{25, 76}

Another group also sought to determine whether there was an effective combination therapy to reduce the shivering threshold in the setting of hypothermia (Table 1).⁴⁶ This study demonstrated a significant and impressive impact on the shivering threshold through the use of meperidine, similar to the results of a previously discussed study.⁴³ In this investigation, however, inhibition of shivering was accomplished without the additive benefit of skin surface warming, and it resulted in respiratory compromise in some volunteers.⁴⁶ Still, the combination of low-dose buspirone and meperidine gave an equivalent level of threshold lowering as that of high-dose meperidine. This implies that the use of buspirone in this setting may provide for a combined dose-sparing effect and lessen the occurrence of adverse effects. The combination of the two therapies did not result in an additive response and was significantly less than what was predicted ($p=0.006$). This may have implications for the mechanisms of actions of these two drugs.

Other Agents

Dantrolene

Since 1975, dantrolene has been recognized as a specific treatment for malignant hyperthermia crises.⁴⁷ However, dantrolene is increasingly being used for emergency treatment of life-threatening hyperthermia that is nonresponsive to conventional treatments. Muscle relaxation is of potential thermoregulatory importance because factors that reduce the efficacy of skeletal muscle activity will similarly reduce the efficacy of shivering and subsequently facilitate hypothermia induction.

Researchers evaluated the effect of dantrolene in two different sets of healthy volunteers on the end points of sweating and shivering thresholds (Table 1).⁴⁷ Shivering was measured in a unique way—by using oxygen consumption rather than clinical diagnosis. 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. It is also difficult to glean much from the results as, although the same dose was used in both groups, the average dantrolene concentration in the first group of volunteers was 5.2–5.6 µg/ml, whereas it was 7.5 µg/ml in the second group. Of interest, dantrolene use reduced the shivering gain, likely due to the peripheral skeletal muscle activity of the drug, which would reduce thermogenesis. This may have wider implications beyond the use of dantrolene and demonstrates the potential efficacy of nondepolarizing neuromuscular blockers.

Propofol

Propofol was initially used as a general anesthetic but now frequently is used for sedation in the critical care arena.⁷⁷ This agent has a rapid offset and extensive tissue penetration.⁷⁸ In one study, five healthy men were randomly assigned on four different days to a control and three different target serum concentrations of propofol (Table 1).⁴⁸ 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. Although no adverse effects were noted, mean arterial pressures were lowered from 97 to 80 mm Hg in the 8-µg/ml group. From a clinical standpoint, the results of this study are difficult to apply as only serum propofol

concentrations and no actual dosages were reported. Patients with hypotension after cardiac arrest may not tolerate propofol at relatively high doses because of its propensity to cause hypotension.

Doxapram

Doxapram was developed in the 1960s and quickly found a role in stimulating respiratory drive.⁷⁹ It stimulates the carotid body in a dose-dependent manner, similar to hypoxemia. Both animal and human models have demonstrated its usefulness in the treatment of postanesthetic shivering.^{80, 81} To evaluate its usefulness outside the surgical setting, one study enrolled nine healthy volunteers on 2 days and gave them either placebo or a doxapram intravenous infusion at a target serum concentration of 4 µg/ml (Table 1).⁴⁹ Information regarding how the patients were warmed and cooled was not provided, which is a major limitation of the research. Although the results were statistically significant, it is unlikely that a decrease of 0.5°C has clinical implications. In addition, the authors did not provide data regarding actual dosing of the drug. However, the study does demonstrate a proof of concept for doxapram and an effect on the shivering threshold. 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.

Comparison and Limitations of the Clinical Study Data

Although still relatively novel, the induction of hypothermia for the preservation of cerebral tissue is becoming more commonplace in major institutions. Questions still remain over the potential benefits and harm that this therapy may cause; however, even more questions exist regarding the ideal method for implementing these protocols and the management of patients during the induction. One such challenge involves the prevention and limitation of homeostatic mechanisms such as thermoregulatory processes that run directly counter to the goal of hypothermia. Several drugs have been used successfully in the operating room but may not be appropriate for the typical patient with out-of-hospital cardiac arrest, and anesthesia has its own effects on thermoregulatory processes. Thus, only evaluations of these drugs conducted in healthy volunteers can be used to determine their efficacy.

Various 5-HT agents, NMDA antagonists, α_2 -agonists, opioids, buspirone, dantrolene, propofol, and doxapram have been studied for the prevention or treatment of hypothermia-induced thermoregulatory responses in the absence of anesthesia. Interpretation of these data is complicated by the various techniques used for induction of hypothermia and lack of comparative studies. In addition, 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.⁸² The available data suggest that, compared with other drugs, α_2 -agonists and opioids may lower the shivering threshold the most. Although potentially limited by hypotension and sedation, both clonidine and dexmedetomidine demonstrated dose-dependent alterations in thermoregulatory thresholds that are potentially clinically relevant (1.6°C and 2.4°C, respectively).^{40, 42} Meperidine has also demonstrated notable effects on the depression of the shivering threshold with a reduction of 1.7–2.3°C.^{43, 45, 46} Nevertheless, none of the therapies has been adequately explored to provide a clear recommendation. In addition, 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.

In addition, multiple nonpharmacologic issues make the optimization of antishivering therapy difficult. 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, a risk for this patient population depending on the extent of its neurologic damage. These diagnostic challenges combined with several therapeutic options make it a unique environment for intense pharmacy involvement.

Directions for 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 in this population have the potential to be more profound and impressive. In addition,

more comparative studies are needed. Trials should be conducted to minimize high drug doses and subsequent adverse effects. The beneficial role of physical interventions such as skin warming also needs to be more thoroughly elucidated so that drug doses can be minimized. Interventions should be standardized across trials to allow for comparative analysis and to enhance isolation of true pharmacologic effects. Furthermore, additional agents that have demonstrated efficacy in the postanesthesia realm warrant exploration, such as nondepolarizing neuromuscular blockers. Finally, the role of the clinical pharmacist in the management of these patients should be explored as this may have a direct impact on patient outcomes.

Conclusion

Interest and data regarding the benefits of therapeutic hypothermia continue to grow. However, the implementation of this therapy is often limited by endogenous thermoregulatory responses, such as shivering, that attempt to return the patient's core temperature to the natural thermoneutral zone. 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. Recent literature has demonstrated significant improvements in neurologic outcomes in patients who have received induced hypothermia in the setting of out-of-hospital cardiac arrest. 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. Among these, clonidine, dexmedetomidine, and meperidine have demonstrated the greatest and most clinically relevant impact on depression of the shivering threshold. Future research in this area should be conducted in patients who have experienced out-of-hospital cardiac arrest; studies should evaluate additional agents, standardize physical interventions, and monitor for adverse effects of the drugs. In addition, the role of the clinical pharmacist in the development and implementation of this therapy needs to be defined, and their impact on patient outcomes should be assessed.

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