

Pharmacological Management of Therapeutic Hypothermia-Induced Shivering

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The role of therapeutic moderate hypothermia (32 to 34°C) has evolved in the past decade and become an essential part of management following post-cardiac arrest resuscitation.¹ Additionally, this practice has gained momentum as a potential neuroprotective measure in patients following acute brain injury. However, achieving and maintaining the target temperature is challenging. The human body maintains a core temperature of $36.6 \pm 0.4^\circ\text{C}$. When body temperature is lowered, the physiologic response is to prevent further heat loss through vasoconstriction. When vasoconstriction is no longer effective, shivering occurs to counterbalance heat loss. In the context of induced hypothermia, shivering is undesirable because it causes patient discomfort and increases body temperature and metabolic demands, resulting in an increased need for oxygen and additional energy sources. Shivering also increases intraocular and intracranial pressures.^{2, 3}

Shivering has been reported in many postoperative cases, but the true incidence is not clearly documented in therapeutic hypothermia. Depending on the method employed for cooling (e.g., surface cooling, endovascular cooling), the incidence has been reported between 8% and 85% despite active prevention in most protocols. Such preventive measures include surface warming (e.g., face, extremities), air warming and pharmacologic interventions. This review focuses on the current pharmacologic modalities for therapeutic hypothermia-induced shivering.

Anesthetics and Sedation

Experience with anesthetic and sedative agents has shown that certain agents can reduce postoperative shivering. Volatile anesthetics, including halothane, isoflurane and enflurane, appear to be thermogenesis inhibitors, causing a reduction in the shivering threshold.^{4, 5} In the intensive care unit, intravenous sedatives provide a more practical approach at the bedside. Propofol is the agent most studied for shivering control.⁶ Several studies compared propofol to either thiopental or isoflurane as induction agents for anesthesia and assessed the impact on postanesthetic shivering.⁷⁻⁹ Significantly fewer patients experienced shivering in the propofol group compared to thiopental alone or thiopental plus isoflurane group. While a single dose of propofol normally is used for anesthesia induction, it is often used as a continuous infusion for induced hypothermia. A few pharmacokinetic studies have reported that during hypothermia, the plasma concentration of propofol is increased by 30% due to reduced clearance.¹⁰ Clinicians should be aware of the altered pharmacokinetics of these drugs during hypothermia and be cautious when titrating doses to avoid unwanted effects such as oversedation and severe respiratory depression.

Opioids and Analgesics

Opioids commonly are used for shivering control during therapeutic hypothermia, with meperidine the most well-described agent for this indication. Compared to other opioids, such as morphine, fentanyl and alfentanil, meperidine appears to be a more effective antishivering agent.^{11,12} Its superiority is suggested partly due to activity at δ -receptors rather than μ -receptors. Additionally, meperidine also may affect NMDA (N-methyl-D-aspartate) receptors, α -receptors, and neurotransmitters including 5-HT (5-hydroxytryptamine) and norepinephrine.^{13,14} Wrench et al reported a dose effect associated with meperidine for postanesthetic shivering control, where the minimum effective dose was 25 mg.¹⁵ Some studies have suggested the need for higher doses of meperidine to lower the shivering threshold to 33.5°C effectively.¹¹ Meperidine also was shown to have a synergistic effect with skin surface warming in reducing this threshold in healthy volunteers.¹⁶ Despite a lack of placebo-controlled randomized studies, meperidine has shown to be effective in shivering control in other comparative trials involving active medications such as buspirone, dexmedetomidine and ondansetron.¹⁷⁻²¹ The concern with the routine use of meperidine is the toxicity, which may cause central nervous system excitation, among other conditions.

Other pure μ -opioid receptor agonists (e.g., morphine, alfentanil, fentanyl) also have been evaluated, primarily in postanesthetic shivering studies.^{12,17, 22-24} Results have been mixed on their efficacy for shivering control.¹² Overall, higher doses of morphine (loading dose 1 to 4 mg/kg, followed by 0.2 to 0.5 mg/kg/hr), alfentanil (250 μg) and fentanyl (1.7 $\mu\text{g}/\text{kg}$) were necessary for effective shivering control, with lower doses proving to be ineffective. Fentanyl weakly binds to the δ -receptor and may require higher concentrations to achieve this effect.¹² As with propofol, an increase in the plasma concentrations was reported with morphine, fentanyl and alfentanil due to a decrease in elimination.²⁵⁻²⁸ These findings suggest therapeutic hypothermia may result in toxicities if not monitored closely. More pharmacokinetic studies are needed to evaluate the effect of hypothermia on drugs commonly used in the critical care unit.

α -Agonists

Thermoregulation through α -receptors is mediated mainly through centrally distributed α_2 -receptors. Clonidine is the most widely studied α -agonist for shivering control. Prophylactic use of clonidine (75 μg intravenous) lowered the threshold of vasoconstriction in healthy volunteers.²⁹ Additionally, a linear relationship between increased clonidine dose (3-9 $\mu\text{g}/\text{kg}$) and greater shivering thresholds was reported.³⁰ In a randomized trial following a single dose of clonidine (0.15 mg intravenous), all

in a randomized trial, following a single dose of clonidine (0.15 mg intravenous), all 20 patients stopped shivering; 16 responded within five minutes.³¹ Comparatively, after receiving one dose of meperidine (25 mg intravenous), 18 of 20 patients stopped shivering, and the remaining two patients responded after the second dose. The average onset of action for meperidine and clonidine was 2.7 and 3.1 minutes, respectively. From these data, clonidine appears to be as effective as meperidine for postanesthetic shivering, but the ability of clonidine to cause bradycardia must be monitored, especially since hypothermia induces bradycardia as well. Dexmedetomidine is a newer α -agonist with an affinity to α_2 - receptors eight times stronger than clonidine. Dexmedetomidine successfully reduced the shivering threshold and vasoconstriction threshold in healthy volunteers.³² In elective surgery patients, dexmedetomidine (1 μ g/kg) given at the time of wound closure significantly reduced postanesthesia shivering (compared to patients who received saline [15% vs. 55%, respectively]) and was comparable to meperidine 0.5 mg/kg (10%).¹⁸ Additionally, dexmedetomidine (target plasma concentration 0.4 ng/mL), when given in combination with meperidine (target plasma concentration 0.3 μ g/mL), appears to offer additive effects in reducing the shivering threshold in healthy volunteers.¹⁹ Compared to the control group (no treatment), dexmedetomidine and meperidine significantly lowered the shivering threshold by 0.7°C and 1.2°C, respectively. Meperidine plus dexmedetomidine, however, reduced the shivering threshold by 2°C. This agent deserves further study for its utility in the clinical setting of moderate hypothermia.

5-HT modulators

The thermoregulatory effect of 5-HT is poorly understood since both hypo- and hyperthermia have been reported. Nevertheless, medications affecting 5-HT have been investigated for their role in reducing shivering during hypothermic therapy. At a 60-mg dose, buspirone – a 5-HT_{1a} partial agonist – reduced the shivering threshold by 0.7°C.²¹ Additionally, a 30-mg dose combined with low-dose meperidine produced a similar reduction in shivering threshold compared to a large dose of meperidine alone (2.3°C).²¹

Also, in the combination group, patients experienced less respiratory depression and sedation than the large-dose meperidine group. These data suggest that buspirone may improve safety when given concurrently with meperidine. Tramadol exerts its analgesic effect through inhibition of norepinephrine and 5-HT reuptake, so it has been studied for postoperative shivering. Studies suggested that tramadol decreased both vasoconstriction and shivering threshold,³³ and was comparable to meperidine for postanesthetic shivering control at the 0.5 mg/kg dose.³⁴ In a randomized trial, a higher dose of tramadol (1 mg/kg intravenously) was more effective in shivering control compared to 0.5 mg/kg meperidine.³⁵

Significantly fewer patients experienced shivering at 10 minutes following injection of tramadol. Ondansetron is a 5-HT₃ antagonist used for nausea and vomiting. When it was given prophylactically at a dose of 8 mg, 15% of patients experienced postoperative shivering compared to 57% in the saline control group.³⁶ Ondansetron also was compared to meperidine in patients with spinal anesthesia.²⁰ The incidence of shivering was similar in the ondansetron- and meperidine-treated groups (8%) and was significantly lower than in the placebo group (36%). Since ondansetron has no hemodynamic or respiratory effects, more clinical trials are warranted to investigate its antishivering effect for induced hypothermia.

Cholinomimetics

The neurotransmitter acetylcholine has been studied for its thermoregulatory effect. In the early 1970s and 1980s, both hypothermic and hyperthermic effects of acetylcholine were reported in various animal studies.³⁷⁻⁴⁰ Scientists believed that the difference in the thermoeffect of acetylcholine likely was due to the activation of different parts of the hypothalamus and different animals.

While the exact mechanism of acetylcholine and thermoregulation has not been delineated, Baird et al demonstrated that direct injection of acetylcholine resulted in decreased shivering through vasodilation in animals.⁴¹ Physostigmine, a cholinesterase inhibitor, was studied for postoperative shivering control in humans⁴²; in a comparative trial, Horn et al found that it significantly reduced shivering compared to placebo, and was comparable to meperidine and clonidine.⁴² More nausea and vomiting were reported in the physostigmine group, but no significant reduction in heart rate was observed. Considering the limited amount of evidence and the potential side effects, such as seizure and respiratory depression, it is difficult to justify its routine role in the management of therapeutic hypothermia-induced shivering.

NMDA Antagonists

Magnesium sulfate has been investigated as an adjunctive therapy to meperidine-based regimens for shivering control. The proposed mechanism of action in magnesium is its antagonistic action on NMDA receptors. Although the exact mechanism is unknown, inhibition of NMDA receptors is associated with reduced release of norepinephrine and 5-HT, which has a thermoregulatory effect. Magnesium sulfate is an attractive choice for shivering control because hypomagnesemia commonly is observed during induced hypothermia. Additionally, magnesium sulfate has been investigated for its neuroprotective property, which may provide additive benefit in patients with brain injury.⁴³⁻⁴⁶ In a study of healthy volunteers, magnesium infusion reduced the shivering threshold by 0.3°C and led to a significant increase in serum magnesium; however, this reduction was not clinically significant in counteracting the shivering effect of therapeutic hypothermia.⁴⁷ In another study, magnesium infusion (4 to 6 g intravenous bolus followed by 1-3 g/hr until rewarming) shortened the time to achieve target temperature and improved patient comfort when added to a meperidine-based regimen (50-100 mg).⁴⁸ Magnesium has also been shown to prevent postoperative shivering.⁴⁹

Ketamine also has NMDA receptor antagonist properties. Low-dose ketamine (0.5 mg/kg) appeared to be effective in the prevention of shivering following general or regional anesthesia compared to placebo^{50,51}; however, its role in induced

hypothermia has not been examined, and caution should be exercised due to its psychomimetic effects such as hallucinations and delirium. In patients with brain injury, ketamine also causes an increase in intracranial pressure and so should be monitored closely.

Miscellaneous Agents

Other medications of interest include neuromuscular blocking agents (NMBA), dantrolene, methylphenidate and doxapram. These agents control the muscular symptoms of shivering, but their use normally is reserved as a last therapeutic option. Hypothermia decreases the clearance of many NMBAs. Studies showed a significant increase in the duration of action of vecuronium, rocuronium and pancuronium, which may result in prolonged paralysis.^{2, 52-54} Most data concerning other agents, including dantrolene, methylphenidate and doxapram, were generated during the perioperative setting. Due to the side effects associated with these medications, their use for therapeutic hypothermia is limited.

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Disclosures

* Author has no disclosures to report