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Physiologic and pharmacologic considerations for hypothermia therapy in neonates

S Zanelli[1], **M Buck**[1,2], and **K Fairchild**[1]

[1]Department of Pediatrics, University of Virginia, Charlottesville, VA, USA

[2]Department of Pharmacy, University of Virginia, Charlottesville, VA, USA

Abstract

With mounting evidence that hypothermia is neuroprotective in newborns with hypoxic-ischemic encephalopathy (HIE), an increasing number of centers are offering this therapy. Hypothermia is associated with a wide range of physiologic changes affecting every organ system, and awareness of these effects is essential for optimum patient management. Lowering the core temperature also alters pharmacokinetic and pharmacodynamic properties of medications commonly used in asphyxiated neonates, necessitating close attention to drug efficacy and side effects. Rewarming introduces additional risks and challenges as the hypothermia-associated physiologic and pharmacologic changes are reversed. In this review we provide an organ system-based assessment of physiologic changes associated with hypothermia. We also summarize evidence from randomized controlled trials showing lack of serious adverse effects of moderate hypothermia therapy in term and near-term newborns with moderate-to-severe HIE. Finally, we review the effects of hypothermia on drug metabolism and clearance based on studies in animal models and human adults, and limited data from neonates.

Keywords

hypothermia; hypoxic-ischemic encephalopathy; neonate; pharmacologic effect; physiology effect; rewarming

Introduction

Until recently, treatment of newborns with hypoxic-ischemic encephalopathy (HIE) was limited to supportive care and pharmacologic treatment of seizures. In the past decade, a number of randomized controlled trials (RCTs) have been published showing that induced hypothermia improves outcomes of infants of ≥36 weeks of gestation with moderate-to-severe acute perinatal HIE.[1–5] Importantly, these studies have demonstrated few significant side effects of moderate induced hypothermia in term and near-term neonates.[6,7]

With increasing numbers of centers offering hypothermia therapy, it is important that caregivers understand the physiologic and pharmacologic effects of lowering core temperature. In this review, we provide an organ system-based assessment of physiologic adaptations to hypothermia and review data from RCTs on the side effects of this therapy in

Correspondence: Dr S Zanelli, Department of Pediatrics, Box 800386, University of Virginia, Charlottesville, VA 22903, USA., sz5d@virginia.edu.

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neonates. We also review the relatively small but growing body of literature on the effects of hypothermia on drug metabolism, clearance and response. Special attention to physiologic and pharmacologic changes is important in all three phases of hypothermia therapy: induction, maintenance and rewarming.

Physiologic effects of hypothermia

A summary of the physiologic effects of hypothermia therapy is provided in Table 1.

Cardiovascular and hemodynamic effects

Much of the evidence of hypothermia effects on the cardiovascular system is derived from animal models or from adult humans with brain injury or undergoing cardiac surgery, in some cases involving core temperatures <30 °C. More recent evidence is emerging from neonatal animal models and from clinical trials in human neonates with temperatures in the mild-to-moderate hypothermia range (32 to 35 °C).

Lowering core temperature results in decreased heart rate, possibly because of the effects on ion transport in cardiomyocytes.[8] In neonates undergoing hypothermia for neuroprotection, heart rate drops by ~14 to 45 b.p.m. and returns to normal on rewarming.[3,5,9] The incidence of heart rate <80 b.p.m. is <5%.[5,10] In adults, moderate hypothermia may cause changes in the electrocardiogram including prolonged PR, QRS and QT intervals, decreased height of T waves and Osborn J waves,[11] but these have not been described in the neonatal population.[12] Although adults may experience atrial fibrillation at temperatures <32 °C and ventricular fibrillation at <30 °C,[13] such arrhythmias have not been described in neonates transiently overcooled to temperatures <30 °C during transport to cooling centers.[14,15]

Hypothermia may cause changes in cardiac contractility and cardiac output (CO). Clinical studies in adult humans have shown that CO decreases by ~7% for every 1 °C drop in core temperature.[16] In a study of seven neonates cooled for perinatal HIE, echocardiography before and after rewarming showed that CO at 33 °C was 67% of that measured following rewarming to 37 °C.[17] No hypotension was noted in these infants, indicating that the decrease in CO matched the decrease in oxygen consumption.

Hypothermia also results in an initial increase in systemic vascular resistance as the body attempts to conserve heat through vasoconstriction.[18] This, combined with release of endogenous catecholamines[18,19] and cortisol[20] due to hypothermic stress, could contribute to an initial increase in blood pressure, particularly in unsedated patients. A pilot study of induced hypothermia in nine asphyxiated neonates reported a median 10 mm Hg increase in blood pressure during cooling and 8 mm Hg fall during rewarming.[21] On the other hand, decreased CO as discussed above and intravascular fluid shifts resulting in hypovolemia could, at least theoretically, result in hypotension during hypothermia. A meta-analysis of five RCTs of hypothermia therapy for perinatal HIE that reported on use of pressors for hypotension found a borderline significant increase in pressor use in hypothermic versus normothermic patients (relative risk 1.17, confidence interval 1.00, 1.38).[10] More recently, investigators from the CoolCaP and NICHD (National Institute of Child Health and Human Development) trials reported no difference in the incidence of hypotension, need for inotropic support or volume resuscitation.[7,22] In general, cardiovascular changes during hypothermia therapy seem to be well tolerated in neonates, with no evidence of significant compromise to organ perfusion.[10,23]

The effect of hypothermia on tissue lactate levels is unclear. Decreased tissue perfusion during hypothermia therapy may theoretically cause lactic acidosis. Although increased lactate levels have been reported in pediatric and neonatal populations,[24–26] neonatal RCTs

did not report an increased incidence of lower blood pH in hypothermic infants.[5,6] This may reflect a proportional decrease in tissue perfusion and demand. In fact, recent experimental evidence suggests that lactate levels correlate with the severity of insult rather than the degree of hypothermia.[27]

Changes in intravascular volume and blood viscosity during hypothermia have been reported in both in vivo and in vitro studies, and these changes could theoretically result in altered hemodynamics and tissue perfusion. In vitro studies show increased blood viscosity with hypothermia due, in part, to decreased deformability of blood cells.[28] With prolonged hypothermia, a decrease in intravascular volume may occur because of fluid shifts and cold-induced diuresis, leading to hemoconcentration.[29] Limited data suggest that these factors are not significant in neonates undergoing therapeutic hypothermia.

Respiratory and blood gas effects

Blood gas values are affected by hypothermia because of increased solubility of gases at lower temperatures and reduced metabolic rate.[30–32] With every 1 °C drop in core temperature, pH increases by 0.016 points. $PaCO_2$ falls because of increased dissolved CO_2 and decreased CO_2 production. In spontaneously breathing patients, this leads to decreased minute ventilation in order to maintain $PaCO_2$ in the normal range. Blood gases measured at actual patient temperature (~33 °C, pH stat method) would show a respiratory alkalosis, whereas blood gases not corrected for patient temperature (37 °C, α-stat method) would show a lower pH and higher CO_2 than actual patient values. With the α-stat method, which has been used in neonatal clinical trials, actual $PaCO_2$ values of a hypothermic patient at 33.5 °C are ~0.83 the value measured on the blood gas at 37 °C.[32] Using α-stat blood gas analysis may result in inadvertent hypocapnia that could decrease cerebral blood flow. For this reason, some experts have recommended targeting PCO_2 in the 40 to 50 mm Hg range in mechanically ventilated infants undergoing hypothermia therapy when blood gases are measured at 37 °C.[33]

The oxyhemoglobin dissociation curve is shifted to the left at lower temperature, resulting in a higher affinity of hemoglobin for oxygen.[34] The resulting decrease in oxygen release to tissues is counterbalanced by decreased tissue oxygen demand at lower temperatures, and consequently tissue oxygen content appears to be maintained.[35] Studies in neonates and pediatric patients have shown that transcutaneous pulse oximetry measurements remain accurate if the skin temperature is >29 °C or core temperature is>31 °C.[36,37]

Pulmonary vascular resistance may be increased at lower core temperatures,[38,39] and infants with perinatal asphyxia are at a high risk for persistent pulmonary hypertension of the newborn. Results of early small pilot studies in neonates suggested that hypothermia may worsen pre-existing persistent pulmonary hypertension of the newborn. In one small study, a fraction of inspired oxygen was increased by 0.14 to maintain adequate oxygenation in neonates cooled for HIE.[21] A randomized pilot study reported increased need for inhaled nitric oxide in hypothermic compared with normothermic infants.[6] Larger studies and meta-analyses have not reported an increased incidence in pulmonary hypertension in neonates randomized to hypothermia therapy for HIE. Nonetheless, clinicians should use caution when cooling infants with severe persistent pulmonary hypertension and high supplemental oxygen requirements.

Metabolic and endocrine effects

For each decrease in core temperature by 1 °C, the basal and cerebral metabolic rates decrease by 5 to 7%, leading to decreased glucose utilization.[40] Hypothermia has been associated with hyperglycemia in adult animal and human studies as a result of decreased

utilization, decreased insulin release and sensitivity, and increased gluconeogenesis and glycogenolysis.[41–43] Increased endogenous catecholamine and cortisol release related to asphyxia or to hypothermia may also contribute to hyperglycemia.[19,44,45] As hyperglycemia has been associated with worse neurological outcomes, it is important to monitor and correct persistent hyperglycemia while avoiding hypoglycemia that also has adverse effects on the injured brain.[46,47] Neonatal clinical trials have found no significant association between hypothermia and hypoglycemia but have not reported on the incidence of hyperglycemia.[10]

It is important to note that hypothermia can induce a stress response in unsedated patients, even those with encephalopathy. In cooled, unsedated adults, the levels of norepinephrine and cortisol rise and shivering occurs that increases the basal metabolic rate and could limit the protective effects of hypothermia therapy. A study in asphyxiated newborn piglets showed that failure to administer anesthetic medications eliminated the neuroprotective benefits of induced hypothermia.[20,48] Although newborns with HIE have impaired thermoregulatory responses and seem to tolerate hypothermia better than older patients, shivering has been noted and administration of narcotics to reduce stress is recommended, with dose adjustments to account for altered drug metabolism at lower core temperature, as discussed below. Routine use of morphine for sedation of infants undergoing hypothermia therapy has been reported in RCTs.[1,49]

Renal and electrolyte effects

Although animal models report alterations in renal perfusion and renal function during hypothermia, RCTs of hypothermia in neonates with birth asphyxia have not found significant differences in urine output or creatinine.[10] Potassium moves into cells as core temperature drops and patients may experience mild hypokalemia. During rewarming, the reverse occurs and it is important to monitor serum potassium in patients with impaired renal function at the time of rewarming. Other imbalances that have been described during hypothermia include hypomagnesemia, hypocalcemia and hypophosphatemia.[50,51] No significant electrolyte disturbances have been reported in RCTs of neonates published to date.[10]

Gastrointestinal effects

Limited studies in animal models and in adult humans have shown unchanged or decreased intestinal perfusion during induced hypothermia.[52–54] As asphyxiated neonates may have suffered intestinal ischemia around the time of birth, and as the effects of hypothermia on intestinal perfusion are not well established, feeding during hypothermia therapy is not recommended. In the large clinical trials of hypothermia therapy, infants were not led during the cooling period and a low rate of necrotizing enterocolitis was reported in both groups (1 to 2%). Low-volume non-nutritive enteral feeding of neonates undergoing hypothermia therapy has been described.[33]

Compromised perfusion to the liver during an asphyxial insult results in elevated serum transaminase levels at or shortly after birth. RCTs showed no difference in transaminase levels in hypothermic versus normothermic infants[5,10,23] whereas smaller trials indicated that hypothermia may have a protective effect against liver dysfunction.[55]

Coagulation system effects

Although no increased risk for bleeding has been demonstrated in RCTs of hypothermia therapy in neonates or adults with ischemia–reperfusion brain injury, it is important to note that even mild hypothermia can have significant effects on blood clotting. Changes in platelet number and function, fibrinolysis and clotting enzyme function have been described.[56,57] It is particularly important to monitor coagulation parameters in patients

undergoing therapeutic hypothermia who have additional risks for hemorrhage such as trauma or surgery.

Hypothermia in the range used in clinical trials for neuroprotection may lower the platelet count and alter platelet activation or aggregation. The lower platelet count may be protective against microvascular sludging related to increased blood viscosity and vasoconstriction at lower core temperatures, as occurs in hibernating animals. Thrombocytopenia ($<150 \times 10^9$ l^{-1}) has been reported to be more common among hypothermic versus normothermic neonates in RCTs,[10] but it is uncommon for the platelet count to drop low enough to require transfusion. Hypothermia has also been shown to affect platelet activation and aggregation.[58–61] Delayed activation of the fibrinolytic system has also been associated with hypothermia and could lead to increased thrombus formation,[62] which could be of particular relevance in hypercoagulable states such as sepsis with disseminated intravascular coagulation. The kinetics of enzymes involved in blood clotting are generally slowed at temperatures <34 °C.[63] However, in RCTs in neonates with HIE, hypothermia has not been associated with prolonged prothrombin time or partial thromboplastin time. It is important to note that the safety of hypothermia therapy in neonates with other risks for hemorrhage such as preterm infants or those with pre-existing severe bleeding or coagulopathy has not been established.

Host defense effects

Hypothermia can affect immune function through impaired neutrophil release and function, decreased leukocyte chemotaxis, suppressed phagocytosis and killing of pathogens and delayed proinflammatory cytokine release.[64–68] In adults, an increased risk of pneumonia with increasing duration of hypothermia has been reported,[69] but this does not appear to be a significant problem if antibiotics are administered. RCTs in neonates with HIE have not found an increased incidence of bacteremia during or following hypothermia therapy.[10] It is generally recommended that neonates who qualify for hypothermia therapy should be treated with antibiotics empirically for several days pending results of blood cultures sent at birth, as chorioamnionitis and sepsis are associated with birth asphyxia.[70]

Neurologic effects

Preclinical animal studies have shown that every 1 °C decrease in temperature causes a 5% decrease in cerebral blood flow and cerebral metabolic rate of oxygen.[71,72] Similar changes have been described in adult humans.[73] There is evidence in infants that an increase in cerebral blood volume is associated with worse outcomes,[74–76] and reduced cerebral blood flow is felt to be a major mechanism of hypothermic neuroprotection by attenuating reperfusion injury and cerebral edema.[77–79] The effects of hypothermia therapy on cerebral perfusion in neonates are largely unknown. In a case report of an infant cooled following HIE, near-infrared spectroscopic measurements suggested an initial increase followed by a decrease in cerebral blood flow during hypothermia therapy, with return to baseline following rewarming.[80]

Electroencephalographic (EEG) studies in adults reveal a decrease in the frequency and amplitude with core temperature <32.5 °C, and electrocortical silence at temperatures <22 °C.[81] The effects of hypothermia on neonatal EEG have been reported to a limited extent. In a small pilot study of neonates undergoing therapeutic hypothermia during extracorporeal membrane oxygenation, no change in amplitude-integrated EEG (aEEG) signal was seen over the temperature range studied (34 to 37 °C).[82] Furthermore, the study of quantitative EEG parameters during the rewarming phase of hypothermia therapy in 10 neonates found no significant differences as temperature increased from 33 to 37 °C.[83] However, it is important to note that hypothermia therapy may alter the predictive value of early aEEG

patterns, as it has been reported that hypothermic infants have delay in return to normal background aEEG patterns compared with normothermic infants.[84] In this study, the positive predictive value of abnormal early (3 to 6 h) aEEG pattern for predicting adverse outcomes was 84% for normothermic infants compared with 59% for hypothermic infants.[84] Persistence of abnormal aEEG patterns beyond 24 h in infants undergoing hypothermia therapy was, however, shown be predictive of poor neurological outcome at 1 year.[85]

Recent neuroimaging studies show that neonates with HIE randomized to hypothermia therapy have less severe magnetic resonance imaging markers of brain injury compared with control patients. In a substudy of 131 patients in the TOBY (Total Body Hypothermia for Neonatal Encephalopathy) trial, patients randomized to hypothermia had decreased lesions in the basal ganglia/thalamus, white matter and posterior limb of the internal capsule and a higher chance of a normal brain magnetic resonance imaging study.[86,87] Another study reported less cortical gray matter signal abnormalities on magnetic resonance imaging in 12 infants with HIE treated with hypothermia compared with 14 normothermic patients.[88] Finally, a study of volumetric and anatomic magnetic resonance imaging in a subset of 14 patients from the NICHD cooling study showed that infants treated with hypothermia therapy had increased volume of subcortical white matter compared to controls.[89]

During rewarming from therapeutic hypothermia, cerebral metabolic rate increases and emergence of seizures has been reported.[33,90,91] These seizures are often subclinical, and therefore consideration should be given to performing continuous EEG monitoring during rewarming. Hyperthermic overshoot on rewarming from therapeutic hypothermia should be carefully avoided because of the known injurious effects of high temperature on the already-injured brain.[92,93] This is an uncommon event in neonates compared with older patients and can be avoided by continued close temperature monitoring after rewarming is complete. Targeting a goal temperature 0.5 °C lower than standard in the initial post-rewarming period may be considered.

Effect of hypothermia on pharmacokinetics, pharmacodynamics and drug effects

Therapeutic hypothermia has the potential to alter the pharmacokinetics and pharmacodynamics of many drugs routinely used in the care of critically ill neonates. Although only limited research has been done in this area, studies suggest that hypothermia may produce pharmacokinetic changes leading to higher serum concentrations and a greater risk for adverse effects.[51,94] The function of cytochrome P450 (CYP450) and other enzymes declines during hypothermia, resulting in reduced drug clearance and longer elimination half-life. Hemodynamic adaptation to temperature, including peripheral vasoconstriction that shunts blood away from muscle, skin and fat, results in a smaller volume of distribution of drugs such as fentanyl, resulting in elevated serum concentrations. Reduced CO and increased vascular resistance produced by hypothermia may reduce blood flow to the liver and kidneys, further altering drug metabolism.

CYP450 enzymes are known to be affected by hypothermia, resulting in reduced clearance of midazolam, fentanyl, propofol, vecuronium, phenytoin, phenobarbital and propranolol.[51,94] A number of hypotheses for the effect of hypothermia on CYP450 enzymes have been proposed, including changes in binding pocket conformation, reduced substrate affinity for P450-binding sites as well as a slowing of the rate of redox reactions performed by CYP450 enzymes.[94] Although not as well studied, the uridine 5^0 diphospho-glucuronosyltransferase activity may also be reduced at lower temperatures, as suggested by the reduction in morphine-6-glucuronide production during morphine administration in patients undergoing therapeutic hypothermia.[95]

Rewarming may also produce significant alterations in pharmacokinetic and pharmacodynamic parameters. Drugs with a large volume of distribution given before the start of hypothermia can be sequestered in peripheral tissues at the onset of hypothermia and may undergo recirculation upon rewarming, exposing the patient to higher serum concentrations and a greater risk of toxicity.[51,94] Agents that had a prolonged elimination half-life during cooling may be cleared much more rapidly during rewarming, as rates of enzymatic activity return to baseline values, placing patients at risk for subtherapeutic serum concentrations and treatment failure.[95]

Recognition of the potential changes induced by therapeutic hypothermia (Table 2) can aid clinicians in drug selection, dosing and monitoring during cooling and rewarming.

Sedatives and analgesics

The most commonly administered sedatives and analgesics given to sick neonates, morphine, fentanyl and midazolam, all exhibit altered pharmacokinetics and pharmacodynamics during hypothermia. The pharmacokinetic profile of morphine was studied in a subset of 16 neonates enrolled in the TOBY study of moderate systemic hypothermia.[96] All patients received a morphine loading dose (50 to 150 $\mu g\ kg^{-1}$) followed by a continuous infusion ranging from 4 to 30 $\mu g\ kg^{-1}\ h^{-1}$, with dose titration based on patient response. The infusion was stopped at 72 h or earlier if the patient was extubated. Despite similar morphine infusion rates and cumulative doses, there was a significant increase in serum morphine concentration in the hypothermic group at 24 to 72 h. At 72 h, morphine was continuing to accumulate in the hypothermia patients but had reached steady state in the normothermic group. Serum morphine concentrations in the toxic range were more common in the hypothermia group and in neonates whose morphine infusion rate was $>10\ \mu g\ kg^{-1}\ h^{-1}$. Although none of the patients exhibited signs of morphine toxicity, there were trends toward longer ventilator use, longer need for vasoactive agents and a lower encephalopathy score at 4 days of age in the hypothermia group. Morphine clearance rate was lower than expected in both groups when compared with previously published values, but the difference was more pronounced in the hypothermia group. The slower clearance rate during hypothermia may have been the result of reduced activity of UDP-glucuronosyltransferase, the enzyme responsible for morphine glucuronidation.

The effects of hypothermia on fentanyl pharmacokinetics have been studied in both humans and animal models. Fentanyl is a high hepatic extraction drug; its clearance is largely dependent on hepatic blood flow. It is extensively metabolized by CYP3A4 (cytochrome P450 3A4), and in normothermic infants it has an elimination half-life of 2 to 3 h. Studies in piglets and in children undergoing deep hypothermia (18 to 25 °C) during cardiac surgery suggest reduction in both volume of distribution and total body clearance of fentanyl during short-term hypothermia. Longer periods of hypothermia have produced similar effects on fentanyl clearance.[97] In a study of piglets given a fentanyl infusion during mild hypothermia (32 °C for 33 h), plasma fentanyl concentrations increased at the end of the cooling period and remained elevated for at least 6 h after rewarming. Hypothermia reduced the cardiac index by an average of 41% in the piglets, altering fentanyl distribution and reducing systemic blood flow. In vitro analysis of hepatic microsomal activity demonstrated a reduction in CYP3A4 activity by ~30% at 32 °C.

Midazolam, like fentanyl, is primarily metabolized through CYP3A4 and would be expected to accumulate during hypothermia. Although there are no studies of neonates, a study of adults undergoing therapeutic hypothermia following traumatic brain injury revealed a significantly higher volume of distribution and slower clearance when body temperature was <35 °C.[95] Clinicians should be aware of the need for careful dose titration to avoid toxicity,

particularly bradycardia and hypotension. Patients should also be closely observed during rewarming, when the rapid decline in midazolam concentration may place patients at risk for benzodiazepine withdrawal or seizures.

Neuromuscular blocking agents

Neuromuscular blocking agents have been used to improve tolerance of mechanical ventilation and to prevent shivering during therapeutic hypothermia in adults. Although there is currently limited information on the use of these agents in neonatal hypothermia, a study in adults demonstrated a significant correlation between core temperature and plasma clearance of vecuronium.[98] Vecuronium is eliminated by P-glycoprotein transport and metabolized by CYP450 enzymes, and the impairment of enzymatic function during hypothermia may explain these results. This suggests the need for either avoidance of neuromuscular blockade or conservative dosing, perhaps with intermittent therapy rather than a continuous infusion, to prevent excessive drug accumulation.

Anticonvulsants

Phenobarbital, the first-line anticonvulsant in the neonatal population, is metabolized by multiple hepatic CYP450 enzymes and may exhibit a slower clearance in hypothermic states as a result of reduced enzymatic activity. Phenobarbital clearance was shown to be reduced in a study of four children undergoing therapeutic hypothermia after traumatic brain injury.[99] Serum concentration monitoring revealed a 48% decrease in the production of phenobarbital metabolites, with a compensatory 52% increase in the excretion of unchanged drug. Perinatal asphyxia is known to significantly prolong phenobarbital half-life, and inducing hypothermia would be expected to further delay elimination.[100] Dosing recommendations have not been established, but administration of standard loading and maintenance doses appears appropriate, with dosage adjustment guided by serum concentration monitoring to minimize the impact of slower clearance. The TOBY trial utilized a regimen with a 20 $\mu g\ kg^{-1}$ loading dose and a maintenance dose of 5 to 10 $\mu g\ kg^{-1} day^{-1}$ without adverse drug effects.[101]

Phenytoin clearance also appears to slow during hypothermia. The pharmacokinetic profile of phenytoin is often difficult to predict because of its nonlinear (saturable) metabolism via hepatic CYP2C9 and CYP2C19 and the ability of other commonly used therapies, such as phenobarbital, to alter its rate of metabolism. In a study of 14 patients aged 15 to 73 years undergoing therapeutic hypothermia to 34 °C, plasma concentrations of phenytoin were significantly higher during hypothermia than after rewarming.[102] Based on these results, it appears that standard phenytoin dosing recommendations may result in drug accumulation and that dosage modification may be necessary to avoid toxicity. Adjustments made during hypothermia, however, may result in subtherapeutic serum concentrations after rewarming, when metabolic function returns to baseline. Administration of intravenous phenytoin during hypothermia may produce additive cardiac depression such as severe bradycardia and hypotension, and close monitoring is indicated.[103]

Topiramate, an anticonvulsant frequently used in children and adults, has been studied as a neuroprotective agent for neonates undergoing hypothermia for HIE.[104] The pharmacokinetic profile of topiramate during hypothermia was recently evaluated in preparation for a larger clinical trial of the efficacy of this therapy.[104] A total of 13 neonates were given 5 $\mu g\ kg^{-1}$ topiramate enterally once daily for 3 days while undergoing either mild (33 to 34 °C) or deep (30 to 33 °C) whole-body hypothermia. Of the neonates, 11 had topiramate concentrations within the therapeutic range (5 to 20 $\mu g\ ml^{-1}$), whereas 2 of the 3 patients undergoing deep hypothermia had elevated levels. Pharmacokinetic parameters were calculated in nine patients. Minimum and maximum serum concentrations as well as

half-life and area under the time-concentration curve were all significantly higher than values reported in infants not undergoing hypothermia. Time to maximum concentration was longer and total body clearance lower, indicating that both absorption and renal elimination were slower in infants undergoing hypothermia.

Vasoactive agents

The most frequently used vasopressors in the neonatal hypothermia trials have been dobutamine and dopamine. Both the CoolCap and NICHD trials reported no difference in the need for vasopressor use between infants in the normothermic group and those undergoing therapeutic cooling.[105] However, a more conservative approach to managing hypothermic patients, with longer duration of pressor therapy, has been reported in several clinical trials.[6,22] At this time, there is no evidence to suggest that a different dosing strategy for vasopressor therapy is needed during or following neonatal therapeutic hypothermia in neonates.

Antibiotics

Infants undergoing therapeutic hypothermia usually receive empiric antibiotic therapy, typically ampicillin and gentamicin. At this time, gentamicin is the only antibiotic that has been studied during hypothermia therapy in neonates in a subanalysis of 55 infants enrolled in the CoolCap trial.[106] All infants were treated with a once-daily dose of 4 to 5 $\mu g\ kg^{-1}$ gentamicin throughout the 72 h study. Trough serum concentrations, obtained before the second dose, were similar between the groups ($2.19 \pm 1.7\ \mu g\ ml^{-1}$ in the hypothermia patients and $2.3 \pm 2.0\ \mu g\ ml^{-1}$ in the normothermic controls). As anticipated, there was a significant correlation between trough gentamicin concentrations and serum creatinine values. It is noteworthy that 40% of the measured trough concentrations were above the recommended $2.0\ \mu g\ ml^{-1}$, suggesting that the dosing strategy used in this study may be excessive for patients with birth asphyxia. A more conservative regimen, consisting of an initial 2.5 to 3 $\mu g\ kg^{-1}$ gentamicin dose with serum level measured at 12 to 24 h to determine clearance and guide subsequent dosing, may reduce the potential for gentamicin toxicity.

Conclusion

With substantial evidence of safety and efficacy, an increasing number of centers are offering hypothermia therapy for neuroprotection in newborns with HIE. Lowering the core temperature can impact hemodynamic status, respiratory physiology, fluid and electrolyte balance and hematologic factors. In addition, pharmacokinetics and pharmacodynamics of a number of drugs commonly used in asphyxiated neonates are affected by hypothermia. Careful attention to physiologic parameters, laboratory tests and drug dosing is essential to assure optimum outcomes for neonates undergoing hypothermia therapy.

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Table 1

Physiologic effects of hypothermia

System	Physiologic effects	Reported clinical effects in neonatal RCTs
Neurologic	↓Cerebral blood flow[73]	No effect on quantified EEG parameters[83,107]
	↓Cerebral metabolic rate[73]	No difference in seizure incidence[7]
	↓EEG amplitude and frequency <32.5 °C[81]	Improved injury markers on brain MRI[87–89]
Cardiovascular	↓HR[108,109]	Decrease in HR by 15–45 b.p.m.[3,5,9]
	↑Systemic vascular resistance[18]	No change in need for pressors or volume expanders[7]
	↓Cardiac output[16]	No change in corrected QT interval[12]
	↓Intravascular volume, hemoconcentration[29]	No significant arrhythmias[5,14,15,36]
	ECG changes (prolonged PR, QRS, QT)[11]	No change in blood viscosity[26]
	Arrhythmias (atrial, ventricular fibrillation)[13]	
Respiratory	↑Pulmonary vascular resistance[38]	No change in PPHN[7,10]
	↑CO_2 and O_2 solubility[30,32]	No change in need for iNO[7,10]
	↓CO_2 production and O_2 consumption	
	↑pH by 0.016 for every 1 °C ↓ in temperature	
	↓ Minute ventilation to maintain normal $PaCO_2$[31]	
Metabolic, endocrine	↓Basal metabolic rate	No hypoglycemia[5,10]
	↓Glucose utilization and insulin release/sensitivity[41,42]	
	↑Catecholamine and cortisol release[18,19,110]	
Renal, fluid and electrolytes	↓Renal perfusion and GFR[111]	No difference in urine output or creatinine[5,10]
	Impaired salt and water reabsorption, diuresis[29]	No hypokalemia or hyperkalemia[5,10]
	↓K^+ (increased uptake into cells)	No increase in hypomagnesemia or hypophasphatemia[10]
	↑K^+ during rewarming[51]	
	↓Calcium, magnesium, phosphorus[50]	
Gastrointestinal	↓Intestinal blood flow[53]	No increase in necrotizing enterocolitis
Hematologic	↓Platelet number	↓Platelet number[10]
	↑Platelet activation and aggregation[56,57]	No difference in PT, PTT
	↑PT, PTT[63]	No increase in bleeding[10,107]
Host defense	Impaired neutrophil release and function[64,65]	No difference in white blood cell or neutrophil number[10]
	↓Leukocyte chemotaxis[67]	No difference in bloodstream infections[10]
	↓Phagocytosis and killing[67]	

Abbreviations: ECG, electrocardiography; EEG, electroencephalography; GFR, glomerular filtration rate; HR, heart rate; iNO, inhaled nitric oxide; PPHN, persistent pulmonary hypertension of the newborn; MRI, magnetic resonance imaging; PT, prothrombin time; PTT, partial thromboplastin time; RCT, randomized controlled trial.

Table 2

Pharmacologic effects of hypothermia

Drug	Populations studied	Effects	Recommendations
Morphine[96,112]	Adult, infant, animal	↓Clearance	Consider lower starting dose, Conservative dose titration
		↑Serum concentrations	
		Potential for decreased efficacy	
Fentanyl[97,113]	Adult, animal	Drug sequestration in periphery	Consider lower starting dose
		↓Volume of distribution	Conservative dose titration
		↓Clearance	Monitor for increased response during rewarming
		↑Serum concentrations	
Midazolam[95]	Adult	↓Clearance	Consider lower starting dose
		↑Volume of distribution	Conservative dose titration
		↑Serum concentrations	Monitor for withdrawal or seizures during rewarming
Vecuronium[98,114]	Adult, infant	↓Clearance	Use lowest effective dose
			Consider periodic discontinuation to allow for movement
Phenobarbital[99]	Child, infant	↓Hepatic metabolism	Monitor serum concentrations and adjust as needed
		↑Excretion of unchanged drug	
Phenytoin[102,103]	Adult, infant	↓Clearance	Consider lower starting dose
		↑Serum concentrations	Monitor serum concentrations and adjust as needed
			Dosage adjustment may be needed during rewarming
Topiramate[104]	Infant	Longer time to max concentration	Once-daily dosing recommended
		↓Clearance	
		↑Serum concentrations	
Gentamicin[106,115,116]	Infant, animal	↓Clearance with renal dysfunction	Consider lower starting dose
		↑Serum concentrations	

↓ decreased; ↑ increased.