THERAPEUTIC HYPOTHERMIA AND TEMPERATURE MANAGEMENT
Volume 6, Number 4, 2016

DOI: 10.1089/ther.2016.0003

Invited Review

Effect of Hypothermia and Targeted Temperature Management on Drug Disposition and Response Following Cardiac Arrest: A Comprehensive Review of Preclinical and Clinical Investigations

Kacey B. Anderson, BS,[1] Samuel M. Poloyac, PharmD, PhD, FCCM,[1]
Patrick M. Kochanek, MD, MCCM,[2] and Philip E. Empey, PharmD, PhD[3]

Targeted temperature management (TTM) has been shown to reduce mortality and improve neurological outcomes in out-of-hospital cardiac arrest (CA) patients and in neonates with hypoxic–ischemic encephalopathy (HIE). TTM has also been associated with adverse drug events in the critically ill patient due to its effect on drug pharmacokinetics (PKs) and pharmacodynamics (PDs). We aim to evaluate the current literature on the effect of TTM on drug PKs and PDs following CA. MEDLINE/PubMed databases were searched for publications, which include the MeSH terms *hypothermia*, *drug metabolism*, *drug transport*, *P450*, *critical care*, *cardiac arrest*, *hypoxic-ischemic encephalopathy, pharmacokinetics*, and *pharmacodynamics* between July 2006 and October 2015. Twenty-three studies were included in this review. The studies demonstrate that hypothermia impacts PK parameters and increases concentrations of cytochrome-P450-metabolized drugs in the cooling and rewarming phase. Furthermore, the current data demonstrate a combined effect of CA and hypothermia on drug PK. Importantly, these effects can last greater than 4–5 days post-treatment. Limited evidence suggests hypothermia-mediated changes in the Phase II metabolism and the Phase III transport of drugs. Hypothermia also has been shown to potentially decrease the effect of specific drugs at the receptor level. Therapeutic hypothermia, as commonly deployed/applied during TTM, alters PK, and elevates concentrations of several commonly used medications. Hypothermia-mediated effects are an important factor when dosing and monitoring patients undergoing TTM treatment.

Keywords: mild hypothermia, targeted temperature management, drug interactions, drug metabolism, cardiac arrest

Introduction

The use of therapeutic hypothermia (TH) as a neuroprotective treatment strategy in critically ill patients has shifted focus over the past decade. From 2000 to 2010 TH use in the ICU increased largely as a result of several randomized control trials (RCTs), which demonstrated a decrease in mortality and an improvement in neurological outcome in cardiac arrest (CA) patients undergoing hypothermia as compared with normothermic treatment (Bernard *et al.*, 2002; Shankaran and Laptook, 2007). As a result, TH was recommended in the American Heart Association Guidelines for adult out-of-hospital CA patients and in neonates with hypoxic–ischemic encephalopathy (HIE) (Nolan *et al.*, 2003).

Subsequently, in the largest hypothermia RCT of targeted temperature management (TTM) strategies to date, no significant difference was seen in the neurological outcomes of adult CA patients who received TH (33°C) versus the milder target of 36°C (Nielsen *et al.*, 2013). These results have raised questions regarding the benefits of cooling to 33°C. Recently, Moler *et al.* (2015) studied the effect of TH (target temperature of 33°C for 48 h) versus controlled normothermia (36.8°C) in children who suffered an out-of-hospital CA. A trend toward improved outcome (12-month survival with favorable neurological outcome as assessed by the Vineland Adaptive Behavioral Scale) was seen with hypothermia versus normothermia ($p = 0.14$) along with mortality ($p = 0.13$). Given that the power of the study to detect the rather

[1]Department of Pharmaceutical Sciences, Center for Clinical Pharmaceutical Sciences, School of Pharmacy, University of Pittsburgh, Pittsburgh, Pennsylvania.
[2]Department of Critical Care Medicine, Safar Center for Resuscitation Research, University of Pittsburgh, Pittsburgh, Pennsylvania.
[3]Department of Pharmacy and Therapeutics, Center for Clinical Pharmaceutical Sciences, School of Pharmacy, University of Pittsburgh, Pittsburgh, Pennsylvania.

demanding target of 20% improvement in outcome was only 42%, some have suggested that this study supports the use of hypothermia in this population—until proven otherwise (Vincent and Taccone, 2015). Thus, TTM at various levels of hypothermia, continues to be recommended to treat out-of-hospital CA patients and for use in neonates with HIE (Callaway *et al.*, 2015a).

As further evidence becomes available, the degree to which we cool patients may increase from the previous target clinical temperature of 32–34°C. Indeed, recent evidence indicates that even a 1°C reduction in temperature induces neuroprotective signaling cascades in neurons in *in vitro* systems (Jackson *et al.*, 2015). However, studies are needed to delineate the specific patients who maximally benefit from hypothermia treatment based on additional considerations, such as severity of injury, organ dysfunction following CA, inflammation, and coadministered medications.

In critically ill patients, adverse drug events (ADEs) occur commonly and can lead to an increase in hospital stay or in some cases even mortality (Vargas *et al.*, 1998; Rothschild *et al.*, 2005). TH may increase risk of ADEs by changing drug disposition. Previously our group published a review on the effects of hypothermia on drug disposition and response, which spanned from 1965 to June 2006 (Tortorici *et al.*, 2007). We concluded that TH alters drug pharmacokinetics (PKs) and pharmacodynamics (PDs); specifically TH leads to elevated drug concentrations due to a decrease in drug metabolism by cytochrome P450s (CYP450) (Tortorici *et al.*, 2007). In this current review, we aim to expand on our previous and other (van den Broek *et al.*, 2010; Zhou and Poloyac, 2011; Sunjic *et al.*, 2015) reviews to investigate the effects of TTM on drug PKs and PDs to provide perspective on the current views surrounding hypothermia-mediated effects on drug disposition in the setting of CA.

Methods

A MEDLINE/PubMed literature search was performed from July 2006 to October 2015. The following MeSH search terms were included in the search *hypothermia*, *drug metabolism*, *drug transport*, *P450*, *critical care*, *cardiac arrest*, *hypoxic-ischemic encephalopathy, pharmacokinetics*, and *pharmacodynamics*. Clinical studies, review articles, short communications, and case reports were evaluated for eligibility. We define TTM as controlled body temperature below the normothermic temperature of 37°C. We define TH as controlled cooling to 32–34°C. The focus of this review is on the application of TH following a CA. Table 1 includes a list of commonly administered drugs in the ICU that may warrant consideration when administering TH following a CA. Studies on the effect of TTM on drug PK and response that were included are summarized in Table 2.

Results

Effects of TTM on drug metabolism

Sedatives/anesthetics

Midazolam. Midazolam is in the benzodiazepine class of drugs and is commonly administered as a sedative in the ICU. Hostler *et al.* (2010) randomized six healthy volunteers to

Table 1. Commonly Administered Drugs in the ICU and Their Elimination Pathway(s)

Elimination pathway	*Drugs*
CYP2C9/CYP2C19	Phenytoin
	Phenobarbital
	Clopidogrel
	Metoprolol
	Morphine
	Codeine and derivatives
	Pantoprazole
	Warfarin
	Omeprazole
	Lansoprazole
CYP2D6	Pentobarbital
	Metoprolol
	Propranolol
CYP3A	Midazolam
	Vecuronium
	Fentanyl
	Lidocaine
	Verapamil
	Diltiazem
	Amlodipine
	Amiodarone
	Nifedipine
	Alprazolam
	Morphine
	Codeine and derivatives
	Carbamazepine
	Rifampin
	Pantoprazole
	Omeprazole
	Lansoprazole
	Diltiazem
	Enalapril
	Ondansetron
	Digoxin
CYP2B6	Propofol
CYP2A6	Dexmedetomidine
CYP1A2	Lidocaine
Phase II glucuronidation/UGT	Morphine
Renal elimination	Gentamicin
	Sotalol
	Atenolol
	Glycopeptides
	Aminoglycosides
	β-Lactams
	Atracurium
	Bretylium
N-acetyltransferase	Procainamide
Multiple CYP450s	Macrolides
	Fluoroquinolones
	Tetracyclines
	Famotidine
	Meperidine
	Ranitidine
	Methyprednisolone
	Prednisone
	Dexamethasone
	Vecuronium

ICU, intensive care unit.

receive 37°C or 4°C saline infusion with or without magnesium. While the lowest temperature achieved in the hypothermic group was 35.4°C, pharmacometric analysis predicted a 11.1% decrease in midazolam clearance (Cl) per each degree Celsius decrease in core body temperature in healthy volunteers (approximately a 44.4% decrease in clearance to a target clinical temperature of around 33°C) (Hostler *et al.*, 2010).

Bjelland *et al.* (2013) investigated the effects of hypothermia on the disposition of midazolam along with several other sedatives and anesthetics (fentanyl, morphine, and propofol) in patients suffering from CA. A total of 15 CA patients who underwent hypothermic treatment to 33–34°C were enrolled in this case–control study and matched to critically ill patients in the ICU, who did not receive hypothermia ($n = 8$). In contrast to Hostler *et al.* (2010), the investigators found no difference in the volume of distribution (V_D), Cl, or elimination half-life ($t_{1/2}$) of midazolam between the hypothermic patients and the normothermic controls. This study involved a relatively small number of subjects with significant interindividual variability in the midazolam time–concentration profiles in both groups.

Furthermore, the duration of hypothermia treatment across the 15 patients varied from 2 to 17 hours, which may have contributed to the large variability in the drug concentration profiles. In a following observational study, Bjelland *et al.* (2014) investigated the effects of rewarming following hypothermia on the drug concentrations of midazolam in eight CA patients. In contrast to their previous study, they reported a 2.9% decrease in midazolam concentrations for every 1°C increase in temperature (11% total decrease from 33°C to 37°C). One important difference in this study was the use of each patient as their own control, which eliminated the high interindividual variability seen in their previous study.

Bastiaans *et al.* (2013) reported no significant difference in the PKs of midazolam between hypothermic patients (33°C) following resuscitation ($n = 9$) versus normothermic, non-resuscitated patients ($n = 8$). Population PK showed no difference in the Cl or V_D of midazolam between the hypothermic and normothermic groups.

Another clinical study, by Welzing *et al.* (2013), investigated the effect of hypothermia on midazolam PK in nine asphyxiated newborns treated with whole-body hypothermia at 32–34°C for 72 hours. Neonates were administered a continuous infusion of midazolam [30–100 μg/(kg·h)]. Population PK analysis was used to calculate the $t_{1/2}$, V_D, and Cl. In this small study, the authors report a midazolam Cl of 2.57 mL/(kg·min) and $t_{1/2}$ of 7.0 hours, which was comparable to literature values in normothermic neonates. Interpretations of this study are limited by a small sample size with high interindividual variability in midazolam metabolism, which makes it difficult to differentiate the effects of hypothermia versus other covariates, such as liver impairment, on the PK of midazolam.

Empey *et al.* (2012) demonstrated a 17.5% decrease in the systemic clearance of midazolam in hypothermic versus normothermic rats following CA. Following asphyxia, rats were cooled to 33°C or maintained under normothermic conditions at 37°C. Midazolam was administered through continuous infusion [1.5 mg/(kg·h)] and temperature was maintained over an 8-hour study duration to reach steady state. Significantly higher midazolam plasma concentrations were achieved in the hypothermic rats versus the normothermic rats. Noncompartmental analysis revealed that the increase in plasma concentrations was due to a 17.5% decrease in systemic clearance following CA.

Overall, the reported effect of TTM on the PK of midazolam varies from none to 11.1% decrease in systemic clearance per degree Celsius. Based on the preponderance of recent evidence, it is clear that the effect of TTM on midazolam PK is much less than that reported originally by Fukuoka *et al.* (2004). The difference between these studies may be attributed to small sample sizes ($n = 8$–15), different patient populations (neonates vs. adults), different disease states (traumatic brain injury [TBI], CA, healthy volunteers), varying duration of hypothermia (2–72 hours) and rewarming (8 hours up to 6 days) protocols, different PK models, and high interindividual variability. Collectively, these results from clinical studies in adults and preclinical evaluations indicate that CYP3A4 metabolism is probably due to a combination of asphyxia and/or hypothermia with the hypothermia effect ranging between none to 11% per degree Celsius change.

Fentanyl. Fentanyl is an analgesic agent that is commonly administered in the ICU, and is often used during TTM. Fentanyl is extensively metabolized by CYP3A4. However, unlike midazolam, it is considered a high-clearance drug in humans. Based on the well-stirred model of hepatic drug clearance, the elimination of a high-clearance drug such as fentanyl should be predominately affected by changes in hepatic blood flow (Pang and Rowland, 1977).

Bjelland *et al.* (2013) reported a 45.5% decrease in the median total clearance of fentanyl in 14 CA patients versus eight case–control-matched critically-ill patients (36–38°C) [median (semi-interquartile range): 726 (230) vs. 1331 (678); $p < 0.05$]. In a subsequent study, Bjelland *et al.* (2014) reported no change in fentanyl concentrations from the hypothermia to rewarming phases. The lack of change in fentanyl concentrations during rewarming, despite significant changes during hypothermia, may be attributed to the long half-life of fentanyl relative to the short duration of rewarming. Since hepatic blood flow was not able to be measured in either of these clinical studies, it is difficult to mechanistically evaluate how temperature changes affected liver blood flow and contributed to overall changes in fentanyl PK. In conclusion, these recent studies in adults are consistent with previous findings, in which reduced CYP3A activity decreased fentanyl metabolism with potentially undefined contribution of hepatic blood flow.

In the same preclinical study in which Empey *et al.* (2012) reported a decrease in midazolam clearance, they also reported a 20.5% decrease in the systemic clearance of fentanyl in hypothermic versus normothermic rats following CA. Enzyme kinetics revealed that the decrease in formation of the Cyp3a-dependent metabolite, norfentanyl, was attributed to an overall decrease in maximal velocity, V_{max}, and not due to a change in enzyme affinity, K_m.

Phenobarbital. Phenobarbital (PB) is a barbiturate indicated for sedation and epilepsy. PB is primarily metabolized in the liver by the cytochrome P450 2C19 (CYP2C19) isoform. Three clinical studies have investigated the effects of hypothermia on PB PK in neonates, a population where PB is commonly used as a first-line agent to prevent neonatal seizures (Filippi *et al.*, 2011; van den Broek *et al.*, 2012; Shellhaas *et al.*, 2013).

TABLE 2. EFFECT OF HYPOTHERMIA ON DRUG PHARMACOKINETICS IN PRECLINICAL AND CLINICAL STUDIES FROM JULY 2006 TO OCTOBER 2015

Drug	*Disease/model*	*Hypothermia protocol*	*Hypothermia PK effects (vs. normothermia)*	*Reference*
Clinical studies				
Midazolam	Healthy volunteers	35.4°C 3 h	↓ Cl	Hostler *et al.* (2010)
Morphine	CA patients	36–38°C, 33–34°C	↑ $t_{1/2}$ and ↓ Cl of morphine, ↔ V_d	Bjelland *et al.* (2013)
Midazolam		12–24 h	↔ Cl midazolam, ↔ V_d, ↔ $t_{1/2}$	
Fentanyl			↓ Cl_{tot} of fentanyl	
Propofol			↓ Cl_{tot} of propofol	
Remifentanil	CA patients	33–34°C	↓ Concs of remifentanil, propofol, and midazolam during rewarming	Bjelland *et al.* (2014)
Propofol		24 h	↔ Conc of fentanyl	
Fentanyl				
Midazolam				
Midazolam	Resuscitated patients	33°C 24 h	↔ Cl, V_1, V_2, or Q	Bastiaans *et al.* (2013)
Midazolam	Asphyxiated neonates	32–34°C 72 h	↔ Cl	Welzing *et al.* (2013)
Phenobarbital	Neonates with HIE	33.5°C 72 h	↑ Plasma concs, ↑ $t_{1/2}$	Filippi *et al.* (2011)
Phenobarbital	Asphyxiated neonates	33.5°C 72 h	↔ Cl, ↔ V_d	van den Broek *et al.* (2012)
Phenobarbital	Neonates with HIE	36–38°C, 33–35°C 72 h	↔ Cl, ↔ V_d	Shellhaas *et al.* (2013)
Phenytoin	Children with severe TBI	36.5–37.9°C, 32–33°C 48 h	↓ V_{max}, ↔ K_m	Empey *et al.* (2013)
Lidocaine	Asphyxiated neonates	33.5°C 72 h	↓ Cl	van den Broek *et al.* (2013)
Gentamicin	Neonates with encephalopathy	37°C, 33–34.5°C 72 h	↔ Serum concs, ↔ Cl	Liu *et al.* (2009)
Gentamicin	Neonates with HIE	33.5°C 72 h	↑ Trough serum cons, ↓ k_e, ↑ $t_{1/2}$, ↓ Cl, ↔ V_d	Mark *et al.* (2013)
Gentamicin	Neonates with HIE	33.5°C 72 h	↓ Cl, ↔ V_d compared with previous reports	Frymoyer *et al.* (2013)
Gentamicin	Neonates with HIE	37°C, 33.5°C 72 h	↑ $t_{1/2}$, ↓k_e, ↓ Cl, ↑ C_{max} and C_{min}, ↑ AUC	Ting *et al.* (2014)
Morphine	Neonates with HIE	33–34°C 72 h	↑ Serum concs, ↑ AUC, ↓ Cl	Roka *et al.* (2008)
Clopidogrel	CA patients	33–34°C 24 h	↓ Clopidogrel-mediated platelet inhibition	Bjelland *et al.* (2010)
Clopidogrel	CA patients	32–34°C 12–24 h	↓ Clopidogrel-mediated platelet inhibition	Ibrahim *et al.* (2014)
Prasugrel			↓ Prasugrel-mediated platelet inhibition	
Ticagrelor			↓ Ticagrelor-mediated platelet inhibition	
Preclinical studies				
Midazolam	CA rats	32.5–33.5°C 8–10 h	↑ Plasma concs of midazolam and fentanyl	Empey *et al.* (2012)
Fentanyl			↓ Cl_s of midazolam and fentanyl ↔ Brain to plasma ratio	
Dexmedetomidine	Piglets with HIE	33.5°C 18–24 h	↑ Plasma concs, ↓ Cl	Ezzati *et al.* (2014)
Midazolam	CA rats	37°C, 32.5–33°C	↓ Cl of midazolam and chlorzoxazone	Zhou *et al.* (2011)
Diclofenac		8 h	↔ Cl of diclofenac or dextromethorphan	

(*continued*)

TABLE 2. (CONTINUED)

Drug	*Disease/model*	*Hypothermia protocol*	*Hypothermia PK effects (vs. normothermia)*	*Reference*
Dextromethorphan			↓ V_1 of midazolam and dextromethorphan and V_2 for chlorzoxazone	
Chlorzoxazone				
PSP	Rats	37°C, 32°C, or 28°C	↑ PSP plasma concs; ↓ PSP Cl	Nishida *et al.* (2007)
ICG		5 h	↑ ICG plasma concs; ↓ ICG Cl	
FD-4			↔ FD-4 Cl	
Digoxin	*In vitro* cell culture	37°C, 32°C, 30°C, 25°C, and 4°C	↓ Activity of ABCB1 drug transporter	Jin *et al.* (2006)
Inulin			↔ In paracellular transport	
Clopidogrel	*In vitro* blood samples from patients with myocardial infarction	37°C, 33°C	↓ Clopidogrel-mediated platelet inhibition	Ferreiro *et al.* (2014)
Aspirin			↔ Aspirin-mediated platelet inhibition	

AUC, area under the curve; CA, cardiac arrest; C_{max}, maximum concentration; C_{min}, minimum concentration; Cl_s, systemic clearance; Cl_{TOT}, total clearance; concs, concentrations; FD-4, fluorescein isothiocyanate–dextran; HIE, hypoxic–ischemic encephalopathy; ICG, indocyanine green; k_e, elimination rate constant; K_m, Michaelis–Menten rate constant; PK, pharmacokinetic; PSP, phenolsulfonaphthalein; Q, intercompartmental clearance; $t_{1/2}$, elimination half-life; TBI, traumatic brain injury; V_1, volume of the central compartment; V_2, volume of the peripheral compartment; V_D, volume of distribution; V_{max}, maximum velocity of metabolism.

Filippi *et al.* (2011) investigated PB PK at two different doses in 19 asphyxiated newborns who were undergoing 72 hours of mild hypothermia to 33.5°C. Noncompartmental analysis of steady-state PB concentrations demonstrated a higher C_{avg}, C_{min}, and C_{max} in the hypothermic neonates as compared with literature values reported for normothermic neonates. Furthermore, the $t_{1/2}$ of PB was 32.1% longer in hypothermic neonates than the average literature values in normothermic neonates ($t_{1/2} = 173.9 \pm 62.5$ h vs. 114–118 h). Additionally, the V_{ss} was also higher than reported values and the Cl was on the lower end of reported values in normothermic neonates. The authors conclude that hypothermia is likely mediating the decrease in PB elimination, but acknowledge that asphyxia may also be contributing to PK changes.

In contrast to Filippi *et al.* (2011), a clinical study performed by van den Broek *et al.* (2012) reported no effect of hypothermia (33.5°C) for 72 hours on PB PK in asphyxiated neonates. This retrospective study identified 31 neonates with HIE who were administered an intravenous loading dose of PB of 20 mg/kg with additional doses administered as needed in subsequent days. PB concentration was measured in a total of 87 plasma samples obtained from the hypothermic phase ($n = 69$) and rewarming and prehypothermic phases ($n = 18$). Population PK analysis showed that temperature did not have a clinically significant effect on the Cl or V_D of PB. Interestingly, van den Broek *et al.* (2012) noted that the Cl of PB in the asphyxiated neonates was reduced compared with those values reported in nonasphyxiated neonates. This was consistent with findings by Gal *et al.* (1984), who reported a reduction in the clearance of asphyxiated neonates by over half compared with nonasphyxiated neonates. Van den Broek *et al.* (2012) postulated that the effect of asphyxia could be predominately driving changes in the PB CL, and the effect of temperature may not have an additional contributing effect. Since the effect of asphyxia on PB PK was not tested by Filippi *et al.* (2011), this could be the main covariate contributing to the discrepancies in conclusions between these two studies.

Shellhaas *et al.* (2013) also found no effect of TTM on the clearance of PB in neonates with HIE. This retrospective study included 20 neonates with HIE who were administered PB and TTM (33.0–35.0°C), and 19 neonates with HIE who were administered PB, but did not undergo TTM. Using a population PK approach, they also found no effect of temperature on the Cl or V_D of PB between the hypothermic and normothermic neonates. Due to the retrospective nature of this study, exact body temperatures and times were not available to include in analysis and, therefore, the authors were unable to compare the exact relationship between dose, PB PK, and body temperature. Instead, the subjects could only be grouped based on hypothermic or normothermic classification.

Collectively, these studies indicate that the PK of PB may be altered in neonates with HIE who are undergoing TTM. However, the driving force behind that change in PK, and the interplay of disease versus temperature, remains to be determined. It appears that the initial findings reported by Filippi *et al.* (2011), which attribute temperature to changes in PB PK, may be confounded by the effect of asphyxia. More recent population PK studies have failed to show an effect of temperature on PB Cl or V_D. It is likely that any effect of hypothermia on PB PK is due to a decrease in CYP2C9 activity, however, the effect of asphyxia on PB PK is well known and any additional contributions due to a temperature-dependent change in CYP2C9 activity seems unlikely. Furthermore, these studies provide evidence for neonates with HIE only, and whether these results extrapolate to older populations in children and adults is still unknown.

Propofol. Propofol is a sedative and analgesic agent commonly used in neurocritical care in the adult ICU. Propofol is predominately metabolized by CYP2B6 with a small amount undergoing glucuronidation by UDP-glucuronosyltransferase 1A9. Two clinical studies have investigated hypothermia on propofol PK since the time of our previous review.

In the same study that investigated midazolam PK by Bjelland *et al.* (2013), the authors also investigated propofol

PK in 14 hypothermic patients suffering from CA. Hypothermic patients had a 23.2% lower clearance of propofol than normothermic patients [median (semi-interquartile range): 2046 (305) vs. 2665 (223) mL/min; $p = 0.035$]. In a subsequent study, Bjelland *et al.* (2014) investigated the concentrations of propofol during rewarming in 14 CA patients. The concentration of propofol decreased 3.1% per degree Celsius increase in body temperature ($\sim$12.4% total change in concentration from 33°C to 37°C) during rewarming. However, no PK parameters were reported in this study. Propofol, like fentanyl, is considered a high-clearance drug and since hepatic blood flow was not measured in either of these two clinical studies, it is difficult to identify the mechanism underlying the reductions in Cl. Collectively, these two studies in adults indicate that hypothermia may decrease propofol clearance due to a combined effect of hepatic blood flow and/or CYP2B6 activity leading to an increase in concentrations.

Dexmedetomidine. Dexmedetomidine is a sedative agent, which has also been shown to exhibit antishivering properties. Dexmedetomidine undergoes extensive hepatic metabolism primarily through CYP2A6 isoform and direct glucuronidation.

To date, one preclinical study in piglets has investigated the effect of TTM on the PK of dexmedetomidine (Ezzati *et al.*, 2014). Nine piglets underwent cerebral hypoxia–ischemia followed by whole-body hypothermia to 33.5°C for 72 hours. Population PK analysis revealed a 32.7% decrease in dexmedetomidine clearance in hypothermic piglets following hypoxia–ischemia. A limitation of this study is that it included only injured piglets undergoing TTM and, therefore, they could not separate out the effects of injury versus temperature on the PK changes of dexmedetomidine. Overall, the decrease in clearance reported in this preclinical study was attributed to combined effects of injury and cooling. Future clinical studies with larger sample size will be needed to determine the contribution of injury and temperature on the PK of dexmedetomidine, particularly given the recent consideration and evaluation of dexmedetomidine as an antishivering agent (Doufas *et al.*, 2003; Callaway *et al.*, 2015b).

Morphine. Morphine is an analgesic that is commonly administered in the ICU. In contrast to many of the drugs discussed so far which undergo Phase I CYP450 metabolism, morphine undergoes Phase II glucuronidation. Since our previous review, two clinical studies have demonstrated an effect of hypothermia on morphine concentrations and PK (Roka *et al.*, 2008; Bjelland *et al.*, 2013). Roka *et al.* (2008) found significantly higher morphine concentrations in hypothermic neonates with HIE as compared with normothermic neonates with HIE. In this observational study, 10 neonates with HIE underwent hypothermic treatment to 33–34°C and 6 neonates with HIE were maintained normothermia. Mean morphine concentrations after 72 hours of cooling were 40.5% higher in the hypothermic group than in the normothermic group (373 ± 125 ng/mL vs. 222 ± 73 ng/mL). Furthermore, the hypothermic group showed a trend in higher morphine area under the curve than in the normothermic group, despite no difference in the morphine infusion rates between groups [$18{,}608 \pm 8384$ ng/(h·mL) vs. $12{,}135 \pm 3481$ ng/(h·mL); $p = 0.051$]. The median morphine clearance was estimated from a subset of patients with samples available at each time point [0.69 mL/(min·kg) vs. 0.89 mL/(min·kg)]; however, the hypothermic group never reached steady state preventing the calculation of a steady-state morphine Cl in this group.

Bjelland *et al.* (2013) reported that the median half-life of morphine was 36.8% higher in ICU patients undergoing hypothermia versus the normothermia group [median (semi-interquartile range): 266 (43) min vs. 168 (11) min]. Furthermore, the median total CL decreased by 28.8% in the hypothermic versus the normothermic group [median (semi-interquartile range): 1201 (283) mL/min vs. 1687 (200) mL/min]. No significant difference in apparent V_D was seen between groups [median (semi-interquartile range): 413 (89) L vs. 435 (28) L]. Collectively, these two clinical studies in adults and neonates indicate that hypothermia decreases morphine Cl, which is likely due to a decrease in the Phase II metabolic glucuronidation pathway. However, as was seen in many of the previous studies, the change in drug PK is most likely a combined effect of injury and temperature. The degree to which each of these factors contributes to changes in drug PK most likely varies across drugs.

Anticonvulsants

Phenytoin. Phenytoin is a commonly administered anticonvulsant, which primarily undergoes hepatic metabolism through CYP2C9 and CYP2C19. The unique PK of phenytoin includes a relatively long half-life and saturable metabolism within the typical therapeutic range. We conducted a clinical study investigating the effects of hypothermia on phenytoin PK in children (ages 2.1–16.2 years) following TBI (Empey *et al.*, 2013). Nineteen children with TBI in a prospective RCT were randomized to receive hypothermia or normothermia treatment. Using a population PK approach, hypothermia was shown to reduce phenytoin elimination. Specifically, hypothermia led to an overall decrease of $\sim$50% in the V_{max} of phenytoin. Importantly, these supratherapeutic phenytoin concentrations remained elevated days after the end of cooling and rewarming and into the posttreatment period. This was a similar finding to Bjelland *et al.* (2014) who reported that temperature effects on fentanyl PK long after the hypothermia phase. Collectively, these results are an important finding with regard to pharmacotherapy and TTM, namely, that drugs with long half-lives, such as phenytoin and fentanyl, when administered to patients undergoing TTM, should continue to be monitored even into the posttreatment period and subsequent dose adjustments should be made accordingly. This is particularly true given that rewarming has been identified as a period of potential heightened hemodynamic and brain instability in brain-injured patients (Hutchison *et al.*, 2008; Abend *et al.*, 2009).

Lidocaine. Lidocaine is an antiarrhythmic agent and is also used as a second or third-line treatment for neonatal seizures. Lidocaine undergoes hepatic metabolism through CYP1A2, and is classified as a high-clearance drug, therefore, its hepatic CI is predominately impacted by changes in hepatic blood flow. Van den Broek *et al.* (2013) investigated the effects of TTM on the PK and efficacy of lidocaine in neonates with encephalopathy. A total of 22 asphyxiated neonates underwent hypothermia to 33.5°C for 72 hours.

Population PK analysis revealed a 24% decrease in lidocaine CI in the hypothermic versus normothermic neonates. The reduction in CI was attributed to a decrease in hepatic blood flow, which is a known physiologic effect of hypothermia. In conclusion, the authors recommend using the same dose of lidocaine in children with a slight decrease in the loading infusion duration by 30 minutes.

Antimicrobials

Gentamicin. Gentamicin is an antimicrobial agent that is administered to treat infections in critically ill patients. Gentamicin is primarily renally eliminated in an unchanged form through glomerular filtration. Since gentamicin is known to be nephrotoxic, blood concentrations are routinely measured in the ICU.

Several clinical studies have investigated the effect of TTM on gentamicin PK in neonates (Liu *et al.*, 2009; Frymoyer *et al.*, 2013; Mark *et al.*, 2013; Ting *et al.*, 2014). Liu *et al.* (2009) was the first to report no significant effect of TTM on the serum gentamicin concentration in neonates with HIE. Trough serum gentamicin concentrations were not different between the hypothermic and normothermic groups (2.19 ± 1.7 mg/L hypothermic vs. 2.30 ± 2.0 mg/L normothermic). However, neonates in both groups had elevated serum concentrations, which can also be explained by the strong correlation between acute kidney dysfunction and elevated gentamicin concentrations. Similar to previous studies, this suggests a potential effect of disease over temperature on the PK of gentamicin. However, no PK parameters were reported in this study.

Mark *et al.* (2013) also investigated the effects of hypothermia on gentamicin PK in neonates with HIE. In this retrospective case–control study, 16 neonates with HIE, who underwent hypothermia (33.5°C for 72 hours) and received at least two doses of gentamicin, were included. Neonates with HIE ($n = 7$), who did not undergo hypothermia treatment, but received at least two doses of gentamicin, were included in the control group. The hypothermic neonates had a 40% increase in half-life (9.16 ± 2.08 hours vs. 6.56 ± 1.81 hours; $p < 0.01$), a 25.5% decrease in Cl [0.04 ± 0.01 L/(kg·h) vs. 0.05 ± 0.01 L/(kg·h); $p < 0.01$], and a 28% decrease in the elimination rate constant k_e (0.08 ± 0.02/h vs. 0.11 ± 0.03/h; $p < 0.01$). The hypothermic neonates also had an average trough gentamicin concentration 2.2 times higher than the normothermic neonates (1.68 ± 0.69 mcg/mL vs. 0.77 ± 0.53 mcg/mL; $p < 0.01$). These findings are consistent with those reported in our previous review by Koren *et al.* (1985), in which the t½ of gentamicin was increased by 39% in hypothermic pigs and the k_{el} and Cl were decreased by 27% and 51%, respectively (Koren *et al.*, 1985). Both the hypothermic study in pigs by Koren *et al.* (1985) and the clinical study by Mark *et al.* (2013) demonstrate a combined effect of injury and temperature on the PKs of gentamicin.

Frymoyer *et al.* (2013) further investigated the effect of hypothermia on gentamicin PK in neonates with HIE. A retrospective chart review identified 29 neonates with HIE (47 gentamicin concentrations) who underwent hypothermia and received an intravenous gentamicin dose of 5 mg/kg Q 24 hours. A population PK analysis was performed to determine the Cl and V_D of gentamicin in this patient population and subsequent simulations were done to determine a dosing regimen that would achieve therapeutic concentrations. Clearance in this patient population was 0.118 L/h, which was 25–50% lower than reported literature values in normothermic neonates with HIE. In contrast, the V_D in the hypothermic neonates was similar to reported values in normothermic neonates. Simulations based on these PK parameters predict a dosing regimen of gentamicin every 36 hours, instead of the typical 24 hours, to achieve concentrations below the recommended 2 mg/L.

Finally, Ting *et al.* (2014) also investigated the effect of TTM on gentamicin PK in neonates with moderate to severe HIE. They identified 15 neonates with HIE who underwent hypothermia and 19 neonates with HIE maintained normothermia. The hypothermic group had a 26.8% longer half-life than the normothermic group (9.57 hours vs. 7.01 hours; $p = 0.007$) and a high number of neonates in the hypothermic group had elevated gentamicin concentrations compared with those in the normothermic group.

The majority of these studies indicate that gentamicin CI is decreased in neonates with HIE who are treated with hypothermia. The results suggest that a decrease in the dose of gentamicin or an increase in the dosing interval may be beneficial when gentamicin is being administered during hypothermia. However, all of these studies have significant limitations: they are retrospective analyses with a relatively small sample size and are mostly in neonates and have a limited number of plasma samples based on what was previously recorded. Furthermore, these studies cannot separate the combined effect of injury and hypothermia on the PK of gentamicin.

Effect of TTM on drug transport

In addition to drug metabolism, drug transporters also play a key role in determining a drug's PK parameters. P-glycoprotein (P-gp) is expressed in tissues such as the liver, kidneys, intestines, and at the blood–brain barrier and is known to transport a number of clinically important drugs. Although less is known about the effect of hypothermia on the transport of drugs, it is reasonable to postulate that active drug transport would be decreased similarly to active drug metabolism, since transporter proteins are temperature sensitive and would undergo a similar inactive response to cooling.

Jin *et al.* (2006) investigated the effect of TTM on the P-gp drug transporter at 37°C, 32°C, 30°C, 25°C, and 4°C in an *in vitro* cell culture study. Radiolabeled probe drugs were used to quantify the overall flux (transport) across the cell monolayers of P-gp-overexpressing cells. The active transport of [^{3}H]digoxin was decreased by $\sim$50% from 37°C to 32°C, whereas no change in the transport of the paracellular marker, [^{14}C]inulin, was seen indicating a decrease in the active drug transport of P-gp. These findings are consistent with a previous preclinical study, which suggest that hypothermia decreases the active processes of renal tubular secretion, but has no effect on the passive process of renal filtration (Nishida *et al.*, 2007). Future studies are still warranted that quantify the absolute change in drug transporter activity and delineate how these changes may contribute to the overall drug PK.

Effect of TTM on pharmacodynamics

In addition to an effect on drug's PK, cooling can also alter a drug's pharmacodynamic properties. More recently, the

effects of hypothermia on the PDs of antiplatelet agents has been investigated.

Antiplatelets. Clopidogrel is a prodrug that is used to prevent platelet aggregation. Unlike the majority of drugs administered in the ICU, clopidogrel is administered orally and depends on metabolic activation by CYP2C19 as well as other CYP450 enzymes. Bjelland *et al.* (2010) investigated the effect of hypothermia on the clopidogrel's efficacy to inhibit platelets. In this prospective study, 25 CA patients received hypothermia (33–34°C) for 24 hours. Patients received a loading dose of clopidogrel of 300 mg orally followed by maintenance doses of 75 mg. Whole blood samples were collected on day 1 ($n = 25$) during the cooling phase and on day 3 ($n = 16$). During hypothermia, the number of blood samples that had a satisfactory effect of clopidogrel was 0/25. One possible explanation may be a decreased metabolic conversion of clopidogrel to its active form during cooling, however, lack of a PK analysis in this study does not rule out this possibility from other potential pharmacodynamic effects such as genetic variants or function of the gastrointestinal tract.

An *in vitro* study by Ferreiro *et al.* (2014) investigated the effect of hypothermia on the pharmacodynamics of clopidogrel and aspirin. In this study, blood samples were obtained from 20 patients who underwent percutaneous coronary intervention and received loading doses of aspirin and clopidogrel. Mild hypothermia to 33°C led to a decrease in clopidogrel-mediated platelet inhibition, while having no effect on the pharmacodynamic response of aspirin.

More recently, Ibrahim *et al.* (2014) investigated the effect of hypothermia on the PDs of three antiplatelet agents, clopidogrel, prasugrel, and ticagrelor, in patients with acute coronary syndrome. In this study, they demonstrated that the platelet-inhibiting effect of all three drugs was significantly decreased under hypothermic conditions. Clopidogrel showed the largest reduction in platelet inhibition in hypothermic versus normothermic groups (hypo vs. normo: $66.39\% \pm 19.1\%$ vs. $33.36\% \pm 22.1\%$; $p < 0.001$). This study concluded that CA patients who are undergoing hypothermia versus normothermia have increased rates of nonresponders to P2Y12 receptor inhibitors, such as clopidogrel, prasugrel, and ticagrelor.

Current evidence indicates that mild hypothermia to 33°C leads to a pharmacodynamic change in drug-mediated platelet response. Specifically, the platelet-inhibitory effect of the P2Y12 receptor inhibitors, clopidogrel, prasugrel, and ticagrelor, is decreased, with clopidogrel showing the most marked change in pharmacodynamics response. However, since clopidogrel requires conversion into its active metabolite by CYP3A and CYP2C9, the increase in clopidogrel nonresponse may be due to a combination of a decrease in metabolic conversion to active drug (PK change) as well as a pharmacodynamic effect. More studies are needed to understand how the effect of hypothermia on platelet activation versus drug metabolism is dictating this change in response.

Interplay of TH and CA

Changes in drug PK during TH may involve the combination of CA and hypothermia-mediated effects, and adjustments for drugs whose Cl is dependent on CYP450 elimination pathways should take both into consideration. Previously our laboratory investigated the interplay of TH and CA on CYP450 pathways in a preclinical study in rats (Zhou *et al.*, 2011). In addition to its sedative use in the ICU, midazolam is also an established cytochrome-P450 3A (CYP3A) probe (Yuan *et al.*, 2002; Eap *et al.*, 2004). Midazolam was administered with diclofenac, chlorzoxazone, and dextromethorphan to probe CYP3A, CYP2C, CYP, and CYP2D activity, respectively. Midazolam Cl decreased in the CA hypothermia rats versus the normothermic shams [681.6 ± 190.0 mL/(kg·h) vs. 1268.8 ± 348.9 mL/(kg·h)], which indicates a combined effect of injury and hypothermia. Similarly, CZN clearance decreased in a hypothermic rat model of CA as compared with sham normothermic rats [229.6 ± 75.6 mL/(kg·h) vs. 561.89 ± 215.9 mL/(kg·h); $p < 0.05$]. In contrast to chlorzoxazone and midazolam, the Cl of diclofenac or dextromethorphan was not significantly different between any of the groups. Two important findings from this study are that (1) the CA and hypothermia-mediated changes are specific to CYP450 isoform and (2) ischemic injury is a significant contributor to reduced metabolism in this injury model producing decreased Cl of chlorzoxazone and midazolam. Future studies should investigate the extent to which injury versus cooling effect drug PK in clinical studies as well as the interplay of these effects on drug PDs.

Discussion

We conducted a thorough PubMed search to identify studies published in July 2006 to October 2015, which investigated the effects of hypothermia on drug disposition and identified 23 studies (6 preclinical and 17 clinical) that investigated the impact of TTM on drug PK and/or PD. With our previous review of 21 studies (8 preclinical and 12 clinical), from 1965 to June 2006, this provides a comprehensive review of the update of TTM on drug PK/PD (Tortorici *et al.*, 2007).

There are several key differences in the cohort of studies published in our previous review as compared with those discussed in this article. Most likely these differences are due to new recommendations for the application of TTM, which have continued to evolve as we learn more about the benefits and risks of cooling patients and the expanding sophistication of PK evaluations in critical care. In our previous review, the depth of cooling varied considerably across preclinical and clinical studies (28–34°C). Nine of the 21 studies cooled to temperatures well below the current optimal target clinical range, to concentrations more likely to be associated with adverse events. In addition, the majority of the patient population included in our previous review was brain-injured patients or healthy volunteers. In this current review the majority of studies consist of CA patients or neonates with HIE, consistent with the two patient populations in which TTM is recommended. Furthermore, over the past 10 years, the need for more robust population PK analysis approaches (pharmacometrics) has been recognized and applied (Poloyac and Empey, 2013). Our previous review reported mostly surveys of drug concentrations rather than true PK evaluations. Recent investigations employed more robust pharmacometric approaches to appropriately investigate the effect of temperature versus other covariates on PK parameters.

Recent studies suggest that the magnitude of change during hypothermia is impacted by the fact that ischemic insults, or changes in physiology such as blood flow, also reduce drug metabolism. As outlined in Table 2, TTM to hypothermic levels decreases Phase I drug metabolism of the CYP450 enzymatic pathways leading to an increase in the blood concentrations of many of these drugs. Recently, it has become clearer that changes in drug PK may be attributed to the interplay of injury and hypothermia. Previously, our laboratory demonstrated that chlorzoxazone and midazolam Cl decreased in a hypothermic rat model of CA as compared with sham normothermic rats (Zhou *et al.*, 2011). Population PK modeling demonstrated that an interaction between hypothermia and CA led to an even greater effect on metabolism than in the presence of either covariate alone. Many clinical studies, such as Filippi *et al.* (2011), speculated that asphyxia was contributing to PK changes in addition to hypothermia. Some studies, such as van den Broek *et al.* (2012), found no effect of temperature on drug PK, but did find changes in Cl parameters in asphyxia neonates when compared with nonasphyxia neonates.

Based on recent evidence evaluating drug concentrations during rewarming and posttreatment phases, the theoretical time course of hypothermia-mediated effects on drug disposition, which was proposed in our previous review, should be revised. We previously described a decrease in CYP450 activity during cooling followed by a return to basal activity following the rewarming phase. However, newer data clearly demonstrate that consequences of metabolic effects may persist even after the rewarming phase and into the posttreatment period, especially for drugs with long half-lives. This was seen in the study by Empey *et al.* (2013) demonstrating prolonged effects of reduced phenytoin elimination well into the posttreatment period. Additionally, Bjelland *et al.* (2014) saw no change in fentanyl concentration during the rewarming phase and attributed it to a possible delay in metabolic changes due to its long half-life. Shellhaas *et al.* (2013) also speculated that PB's long half-life may attribute to changes even after rewarming. Heightened awareness and increased monitoring of hypothermia effects should thus be taken into consideration both when cooling initiated when medication taken at home before CA may persist in the system and after cooling is stopped and during the rewarming and posttreatment phases, particularly for drugs with long half-lives.

In the largest RCT of TTM to date, Nielson *et al.* (2013) reported that cooling to 36°C versus 33°C does not have a significant difference on the outcome of out-of-hospital CA patients. These results suggest that the degree to which adult CA patients are cooled may lessen, which could potentially diminish the effects of cooling on drug disposition. However, as seen in the findings and interpretation of the recent pediatric out-of-hospital CA study, currently, many centers continue to cool adult and pediatric CA patients to 33–34°C and TH remains the standard of care in term neonatal HIE patients.

In conclusion, recent data confirm that hypothermia, such as that employed during TTM, alters PK, and elevates drug concentrations for several medications commonly used in the intensive care unit. Following a CA, patients are at high risk for hypothermia/injury-mediated effects on PK from the large number of medications administered (Table 1). The current data demonstrate a combined effect of hypothermia and CA on drug PK and response. In contrast to earlier studies, recent clinical investigations have (1) incorporated robust PK methods such as pharmacometrics, (2) conducted experiments using recommended clinical protocols (degree of cooling and duration of cooling/rewarming), and (3) incorporated appropriate comparator/control groups.

Clinical studies are ongoing to evaluate specific dosing regimens in critically ill patients undergoing TTM across various levels of hypothermia (clinicaltrials.gov; NCT 01560338, NCT02546947, NCT02529202, NCT02621944, NCT02252848). Future studies should include drugs commonly used in patients following CA (Table 1), such as, meperidine, or that may be chronic medications in this population (taken at home before hospitalization), which have not been investigated during TH. The effect of hypothermia and injury on drug disposition continues to be an important consideration when dosing and monitoring patients undergoing targeted TTM. Finally, additional well-designed studies evaluating the impact of hypothermia on drug transport and pharmacodynamics are needed.

Acknowledgment

Grant support was provided by the National Institutes of Health award KL2TR000146 (P.E.E.).

Author Disclosure Statement

No competing financial interests exist.

References

Abend NS, Topjian A, Ichord R, Herman ST, Helfaer M, Donnelly M, Nadkarni V, Dlugos DJ, Clancy RR. Electroencephalographic monitoring during hypothermia after pediatric cardiac arrest. Neurology 2009;72:1931–1940.

Bastiaans DE, Swart EL, van Akkeren JP, Derijks LJ. Pharmacokinetics of midazolam in resuscitated patients treated with moderate hypothermia. Int J Clin Pharm 2013;35:210–216.

Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, Smith K. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 2002;346:557–563.

Bjelland TW, Hjertner O, Klepstad P, Kaisen K, Dale O, Haugen BO. Antiplatelet effect of clopidogrel is reduced in patients treated with therapeutic hypothermia after cardiac arrest. Resuscitation 2010;81:1627–1631.

Bjelland TW, Klepstad P, Haugen BO, Nilsen T, Dale O. Effects of hypothermia on the disposition of morphine, midazolam, fentanyl, and propofol in intensive care unit patients. Drug Metab Dispos 2013;41:214–223.

Bjelland TW, Klepstad P, Haugen BO, Nilsen T, Salvesen O, Dale O. Concentrations of remifentanil, propofol, fentanyl, and midazolam during rewarming from therapeutic hypothermia. Acta Anaesthesiol Scand 2014;58:709–715.

Callaway CW, Donnino MW, Fink EL, Geocadin RG, Golan E, Kern KB, Leary M, Meurer WJ, Peberdy MA, Thompson TM, Zimmerman JL. Part 8: Post-Cardiac Arrest Care: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2015a;132:S465–S482.

Callaway CW, Elmer J, Guyette FX, Molyneaux BJ, Anderson KB, Empey PE, Gerstel SJ, Holquist K, Repine MJ, Rittenberger JC. Dexmedetomidine reduces shivering during mild hypothermia in waking subjects. PLoS One 2015b;10:e0129709.

Doufas AG, Lin CM, Suleman MI, Liem EB, Lenhardt R, Morioka N, Akca O, Shah YM, Bjorksten AR, Sessler DI. Dexmedetomidine and meperidine additively reduce the shivering threshold in humans. Stroke 2003;34:1218–1223.

Eap CB, Bouchoux G, Powell Golay K, Baumann P. Determination of picogram levels of midazolam, and 1- and 4-hydroxymidazolam in human plasma by gas chromatography-negative chemical ionization-mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci 2004;802:339–345.

Empey PE, de Mendizabal NV, Bell MJ, Bies RR, Anderson KB, Kochanek PM, Adelson PD, Poloyac SM. Therapeutic hypothermia decreases phenytoin elimination in children with traumatic brain injury. Crit Care Med 2013;41:2379–2387.

Empey PE, Miller TM, Philbrick AH, Melick JA, Kochanek PM, Poloyac SM. Mild hypothermia decreases fentanyl and midazolam steady-state clearance in a rat model of cardiac arrest. Crit Care Med 2012;40:1221–1228.

Ezzati M, Broad K, Kawano G, Faulkner S, Hassell J, Fleiss B, Gressens P, Fierens I, Rostami J, Maze M, Sleigh JW, Anderson B, Sanders RD, Robertson NJ. Pharmacokinetics of dexmedetomidine combined with therapeutic hypothermia in a piglet asphyxia model. Acta Anaesthesiol Scand 2014;58:733–742.

Ferreiro JL, Sanchez-Salado JC, Gracida M, Marcano AL, Roura G, Ariza A, Gomez-Lara J, Lorente V, Romaguera R, Homs S, Sanchez-Elvira G, Teruel L, Rivera K, Sosa SG, Gomez-Hospital JA, Angiolillo DJ, Cequier A. Impact of mild hypothermia on platelet responsiveness to aspirin and clopidogrel: an in vitro pharmacodynamic investigation. J Cardiovasc Transl Res 2014;7:39–46.

Filippi L, la Marca G, Cavallaro G, Fiorini P, Favelli F, Malvagia S, Donzelli G, Guerrini R. Phenobarbital for neonatal seizures in hypoxic ischemic encephalopathy: a pharmacokinetic study during whole body hypothermia. Epilepsia 2011;52:794–801.

Frymoyer A, Meng L, Bonifacio SL, Verotta D, Guglielmo BJ. Gentamicin pharmacokinetics and dosing in neonates with hypoxic ischemic encephalopathy receiving hypothermia. Pharmacotherapy 2013;33:718–726.

Fukuoka N, Aibiki M, Tsukamoto T, Seki K, Morita S. Biphasic concentration change during continuous midazolam administration in brain-injured patients undergoing therapeutic moderate hypothermia. Resuscitation 2004;60:225–230.

Gal P, Toback J, Erkan NV, Boer HR. The influence of asphyxia on phenobarbital dosing requirements in neonates. Dev Pharmacol Ther 1984;7:145–152.

Hostler D, Zhou J, Tortorici MA, Bies RR, Rittenberger JC, Empey PE, Kochanek PM, Callaway CW, Poloyac SM. Mild hypothermia alters midazolam pharmacokinetics in normal healthy volunteers. Drug Metab Dispos 2010;38:781–788.

Hutchison JS, Ward RE, Lacroix J, Hébert PC, Barnes MA, Bohn DJ, Dirks PB, Doucette S, Fergusson D, Gottesman R, Joffe AR, Kirpalani HM, Meyer PG, Morris KP, Moher D, Singh RN, Skippen PW. Hypothermia therapy after traumatic brain injury in children. N Engl J Med 2008;358:2447–2456.

Ibrahim K, Christoph M, Schmeinck S, Schmieder K, Steiding K, Schoener L, Pfluecke C, Quick S, Mues C, Jellinghaus S, Wunderlich C, Strasser RH, Kolschmann S. High rates of prasugrel and ticagrelor non-responder in patients treated with therapeutic hypothermia after cardiac arrest. Resuscitation 2014;85:649–656.

Jackson TC, Manole MD, Kotermanski SE, Jackson EK, Clark RS, Kochanek PM. Cold stress protein RBM3 responds to temperature change in an ultra-sensitive manner in young neurons. Neuroscience 2015;305:268–278.

Jin JS, Sakaeda T, Kakumoto M, Nishiguchi K, Nakamura T, Okamura N, Okumura K. Effect of therapeutic moderate hypothermia on multi-drug resistance protein 1-mediated transepithelial transport of drugs. Neurol Med Chir (Tokyo) 2006;46:321–327; discussion 327.

Koren G, Barker C, Bohn D, Kent G, Biggar WD. Influence of hypothermia on the pharmacokinetics of gentamicin and theophylline in piglets. Crit Care Med 1985;13:844–847.

Liu X, Borooah M, Stone J, Chakkarapani E, Thoresen M. Serum gentamicin concentrations in encephalopathic infants are not affected by therapeutic hypothermia. Pediatrics 2009;124:310–315.

Mark LF, Solomon A, Northington FJ, Lee CK. Gentamicin pharmacokinetics in neonates undergoing therapeutic hypothermia. Ther Drug Monit 2013;35:217–222.

Moler FW, Silverstein FS, Holubkov R, Slomine BS, Christensen JR, Nadkarni VM, Meert KL, Clark AE, Browning B, Pemberton VL, Page K, Shankaran S, Hutchison JS, Newth CJ, Bennett KS, Berger JT, Topjian A, Pineda JA, Koch JD, Schleien CL, Dalton HJ, Ofori-Amanfo G, Goodman DM, Fink EL, McQuillen P, Zimmerman JJ, Thomas NJ, van der Jagt EW, Porter MB, Meyer MT, Harrison R, Pham N, Schwarz AJ, Nowak JE, Alten J, Wheeler DS, Bhalala US, Lidsky K, Lloyd E, Mathur M, Shah S, Wu T, Theodorou AA, Sanders RC, Jr., Dean JM. Therapeutic hypothermia after out-of-hospital cardiac arrest in children. N Engl J Med 2015;372:1898–1908.

Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, Horn J, Hovdenes J, Kjaergaard J, Kuiper M, Pellis T, Stammet P, Wanscher M, Wise MP, Åneman A, Al-Subaie N, Boesgaard S, Bro-Jeppesen J, Brunetti I, Bugge JF, Hingston CD, Juffermans NP, Koopmans M, Køber L, Langørgen J, Lilja G, Møller JE, Rundgren M, Rylander C, Smid O, Werer C, Winkel P, Friberg H. Targeted temperature management at 33°C versus 36°C after cardiac arrest. N Engl J Med 2013;369:2197–2206.

Nishida K, Okazaki M, Sakamoto R, Inaoka N, Miyake H, Fumoto S, Nakamura J, Nakashima M, Sasaki H, Kakumoto M, Sakaeda T. Change in pharmacokinetics of model compounds with different elimination processes in rats during hypothermia. Biol Pharm Bull 2007;30:1763–1767.

Nolan JP, Morley PT, Hoek TL, Hickey RW. Therapeutic hypothermia after cardiac arrest. An advisory statement by the Advancement Life support Task Force of the International Liaison committee on Resuscitation. Resuscitation 2003;57:231–235.

Pang KS, Rowland M. Hepatic clearance of drugs. I. Theoretical considerations of a ''well-stirred'' model and a ''parallel tube'' model. Influence of hepatic blood flow, plasma and blood cell binding, and the hepatocellular enzymatic activity on hepatic drug clearance. J Pharmacokinet Biopharm 1977;5:625–653.

Poloyac SM, Empey PE. Drug dosing during hypothermia: to adjust, or not to adjust, that is the question. Pediatr Crit Care Med 2013;14:228–229.

Roka A, Melinda KT, Vasarhelyi B, Machay T, Azzopardi D, Szabo M. Elevated morphine concentrations in neonates treated with morphine and prolonged hypothermia for hypoxic ischemic encephalopathy. Pediatrics 2008;121:e844–e849.

Rothschild JM, Landrigan CP, Cronin JW, Kaushal R, Lockley SW, Burdick E, Stone PH, Lilly CM, Katz JT, Czeisler CA, Bates DW. The Critical Care Safety Study: the incidence and nature of adverse events and serious medical errors in intensive care. Crit Care Med 2005;33:1694–1700.

Shankaran S, Laptook AR. Hypothermia as a treatment for birth asphyxia. Clin Obstet Gynecol 2007;50:624–635.

Shellhaas RA, Ng CM, Dillon CH, Barks JD, Bhatt-Mehta V. Population pharmacokinetics of phenobarbital in infants with neonatal encephalopathy treated with therapeutic hypothermia. Pediatr Crit Care Med 2013;14:194–202.

Sunjic KM, Webb AC, Sunjic I, Pala Creus M, Folse SL. Pharmacokinetic and other considerations for drug therapy during targeted temperature management. Crit Care Med 2015;43:2228–2238.

Ting JY, Kwan E, McDougal A, Osiovich H. Pharmacokinetics of gentamicin in newborns with moderate-to-severe hypoxic-ischemic encephalopathy undergoing therapeutic hypothermia. Ind J Pediatr 2015;82:119–125.

Tortorici MA, Kochanek PM, Poloyac SM. Effects of hypothermia on drug disposition, metabolism, and response: a focus of hypothermia-mediated alterations on the cytochrome P450 enzyme system. Crit Care Med 2007;35:2196–2204.

van den Broek MP, Groenendaal F, Egberts AC, Rademaker CM. Effects of hypothermia on pharmacokinetics and pharmacodynamics: a systematic review of preclinical and clinical studies. Clin Pharmacokinet 2010;49:277–294.

van den Broek MP, Groenendaal F, Toet MC, van Straaten HL, van Hasselt JG, Huitema AD, de Vries LS, Egberts AC, Rademaker CM. Pharmacokinetics and clinical efficacy of phenobarbital in asphyxiated newborns treated with hypothermia: a thermopharmacological approach. Clin Pharmacokinet 2012;51:671–679.

van den Broek MP, Rademaker CM, van Straaten HL, Huitema AD, Toet MC, de Vries LS, Egberts AC, Groenendaal F. Anticonvulsant treatment of asphyxiated newborns under hypothermia with lidocaine: efficacy, safety and dosing. Arch Dis Child Fetal Neonatal Ed 2013;98:F341–F345.

Vargas E, Simon J, Martin JC, Puerro M, Gonzalez-Callejo MA, Jaime M, Gomez-Mayoral B, Duque F, Gomez-Delgado A, Moreno A. Effect of adverse drug reactions on length of stay in intensive care units. Clin Drug Investig 1998;15:353–360.

Vincent JL, Taccone FS. Difficulty interpreting the results of some trials: the case of therapeutic hypothermia after pediatric cardiac arrest. Crit Care 2015;19:391.

Welzing L, Junghaenel S, Weiss V, Roth B, Mueller C, Wiesen MH. Disposition of midazolam in asphyxiated neonates receiving therapeutic hypothermia—a pilot study. Klin Padiatr 2013;225:398–404.

Yuan R, Madani S, Wei XX, Reynolds K, Huang SM. Evaluation of cytochrome P450 probe substrates commonly used by the pharmaceutical industry to study in vitro drug interactions. Drug Metab Dispos 2002;30:1311–1319.

Zhou J, Empey PE, Bies RR, Kochanek PM, Poloyac SM. Cardiac arrest and therapeutic hypothermia decrease isoform-specific cytochrome P450 drug metabolism. Drug Metab Dispos 2011;39:2209–2218.

Zhou J, Poloyac SM. The effect of therapeutic hypothermia on drug metabolism and response: cellular mechanisms to organ function. Expert Opin Drug Metab Toxicol 2011; 7:803–816.

Address correspondence to:
Philip E. Empey, PharmD, PhD
Department of Pharmacy and Therapeutics
Center for Clinical Pharmaceutical Sciences
School of Pharmacy
University of Pittsburgh
205 Salk Pavilion
335 Sutherland Drive
Pittsburgh, PA 15261

E-mail: pempey@pitt.edu