Chapter 9

Therapeutic Hypothermia: Implications on Drug Therapy

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1. Introduction

1.1. Overview of drug disposition and response in critically ill patients

Therapeutic hypothermia has been growing in use over the past several years. Proven efficacy of therapeutic hypothermia in pediatric hypoxic-ischemic encephalopathy (HIE) patients and adult out-of-hospital cardiac arrest (CA) patients has led to expanding clinical implementation in both large and small hospitals. Furthermore, its use to control intracranial pressure (ICP) in brain injured patients, as well as ongoing experimental studies for a variety of other conditions, have led to increased use of therapeutic hypothermia in the intensive care unit (ICU). With increased implementation comes a growing need to understand the ramifications of therapeutic hypothermia on other important factors of ICU care. One such factor is drug disposition and efficacy changes in the hypothermic patient. Specifically, clinical practitioners have postulated the question, "Should drug doses be altered during or after cooling in patients receiving therapeutic hypothermia?" The purpose of this chapter is to explore this question and present the current understanding of the effects of mild therapeutic hypothermia on the processes of absorption, distribution, metabolism and excretion, as well as provide specific evidence of drugs with altered and unaltered pharmacokinetics.

The question of altered drug disposition and response in patients receiving therapeutic hypothermia is particularly important due to the wide array of drugs used in critically ill patients. Critically ill patients are known to have a high rate of adverse drug events. This high rate of adverse drug events is due, in part, to the plethora of medications used for analgesia/sedation, paralysis, control of seizure activity, blood pressure, treatment of arrhythmias, control of blood clotting, antibiotics, and delirium prevention. Table 1 provides a list and details the pharmacokinetic characteristics of the medications commonly administered to critically ill patients organized by class of compound. From this table, it is

clear that many of these drugs have large volumes of distribution, are extensively bound to plasma proteins, and require hepatic metabolism as a primary mechanism of elimination.

2. Physiologic effects of therapeutic hypothermia

Before discussing the specific effects of therapeutic hypothermia on drug disposition and response, it is important to first recognize the general physiologic changes that occur in therapeutic hypothermia patients during induction, maintenance, and rewarming. In a broad sense, therapeutic hypothermia is defined as a core temperature less than 35.0˚C. Moreover, there are different degrees of hypothermia which incur a range of neuroprotection and adverse physiologic effects. Hypothermia can be divided based on the degree of cooling and include mild hypothermia, moderate hypothermia, and severe hypothermia. It is generally accepted that mild hypothermia occurs when a subject is cooled to a temperature of 32-34˚C whereas moderate hypothermia is at a temperature range of 30 – 32˚C. Severe, or "deep" hypothermia, is defined as cooling to a temperature below 30˚C. Furthermore, therapeutic hypothermia undergoes different lengths of cooling depending on the subject population. Adult cardiac arrest patients typically undergo therapeutic hypothermia for 24-48 hours, whereas neonates with HIE are cooled for 72 hours. The duration of cooling is largely based on the design of randomized control trials which demonstrated outcome benefits.

Although these temperatures tend to be generally accepted, it is important to note that these categories can be arbitrary across studies and require verification of temperature and duration in the currently published literature. In order to normalize the temperatures discussed in this chapter, we have focused predominately on the effects seen within mild hypothermia (32-34˚C), since this is the clinically relevant temperature range that has been proven to afford neuroprotection without adverse physiologic consequences to patients in the ICU.

a. Cardiovascular effects

Hemodynamic Effects: Hypothermia has been linked to changes in myocardial function. Mild hypothermia induces a decrease in heart rate, but produces an overall increase in the contractility of the heart in sedated patients. Systolic function will improve, but diastolic function may decrease. Some patients may experience an increase in blood pressure while others may see no change in blood pressure. Overall, cardiac output will decrease along with the heart rate. However, the subsequent hypothermia-induced decrease in metabolic demand tends to equal or exceed the decrease in cardiac output, thus keeping the balance between supply and demand constant. Generally, cold diuresis occurs early during cooling and is of a relatively short duration.

In some cases, the heart rate may be artificially increased by drugs or external pacing. However, the effect of hypothermia on myocardial contractility has convoluted results under artificial stimulation. Two pre-clinical studies showed that under normothermic conditions an increase in heart rate led to an increase in cardiac output and myocardial

contractility. In contrast, when heart rate was increased under mild hypothermic conditions there was a decrease in myocardial contractility. The same results were reported in a clinical study in patients undergoing cardiac surgery. When heart rate was not increased artificially, mild hypothermia improved myocardial contractility. Thus, in most patients heart rate should be allowed to decrease with temperature without any serious adverse complications.

Electrocardiographic Effects: Mild hypothermia has also been associated with abnormal heart rhythms. During cooling, hypothermia causes an increase in plasma norepinephrine levels and activation of the sympathetic nervous system. This leads to constriction of peripheral vessels and a shift of the blood from small, peripheral veins to centrally located veins in the core compartment of the body. Ultimately, this results in an increase in venous return which leads to mild sinus tachycardia. As temperature continues to drop even further below 35˚C, the heart rate begins to slow to a below normal rate eventually leading to what is known as sinus bradycardia. The heart rate will continue to decrease progressively as temperature drops to 33˚C and below. The mechanism behind this is a decrease in the rate of spontaneous depolarization of cardiac cells in combination with prolonged duration of action potentials. These electrocardiogram changes usually do not require treatment and in most cases a patient's heart rate should be allowed to decrease with cooling.

Furthermore, some studies have linked hypothermia to an increased risk for arrhythmias. However, hypothermia-induced arrhythmias generally only apply to moderate to deep hypothermia, particularly when temperatures reach less than 30°C. During deep hypothermia, a patient is at higher risk to develop atrial fibrillation or ventricular fibrillation if temperatures reach as low as 28°C. Since temperatures are maintained at greater than 30°C in the ICU, few cases of hypothermia-induced arrhythmias have been observed in clinical trials evaluating the safety of mild therapeutic hypothermia.

b. Renal effects

Therapeutic hypothermia also has physiologic effects on renal function. During cooling, an increase in urinary output, known as cold diuresis, may occur. Cold diuresis results from a combination of an increase in venous return, a decrease in antidiuretic hormone, tubular dysfunction, and decreased levels of antidiuretic hormone and renal antidiuretic hormone receptor levels.

Renal elimination can be divided into passive filtration, active tubular secretion and active tubular reabsorption. Passive glomerular filtration does not seem to be affected by therapeutic hypothermia. One clinical study investigated the effects of mild hypothermia on renal filtration by measuring serum creatinine levels and creatinine clearance in subjects with and without hypothermic treatment. The study found no change in creatinine clearance between the two groups and concluded that cooling does not impair renal filtration.

Although passive processes of renal filtration do not seem to be significantly altered, some published evidence does suggest that the active processes of tubular secretion and reabsorption may be altered by mild hypothermia. To date, the effect of therapeutic

hypothermia on the active process of tubular secretion has only been studied preclinically in rats. This study used fluorescein isothiocyanate (FITC)-dextran to measure glomerular filtration and phenolsulfonphthalein (PSP) to measure renal tubular secretion in mildly hypothermic versus normothermic rats. The results showed no change in FITC-dextran clearance, but a significant change in the renal clearance of PSP. These results provide further evidence that the passive process of renal filtration is unaffected by mild hypothermia, whereas, active renal tubular secretion is decreased during cooling. There are, however, a limited number of studies published to date and whether or not these initial evaluations remain true clinically will depend on more extensive assessments of the effects of mild hypothermia on renal drug elimination processes.

c. Electrolyte effects

Therapeutic hypothermia also alters electrolyte levels such as magnesium, potassium, and phosphate. During cooling, electrolytes shift from the bloodstream to the intracellular compartment. The low level of electrolytes remaining in the bloodstream increases a patients risk for hypokalemia. During rewarming, the opposite effect is seen and potassium, as well as other electrolytes, is released back into the bloodstream from the intracellular compartment. If the patient is rewarmed too quickly, potassium levels will increase abruptly in the bloodstream and the patient may become hyperkalemic. To avoid hyperkalemia, a slow and consistent rewarming period is necessary to allow the kidneys to excrete the excess potassium. Furthermore, frequent lab electrolyte assessments are needed to account for shifts in systemic electrolyte concentrations.

d. Body metabolism & drug clearance effects

Hypothermia has been shown to decrease the metabolic rate by approximately 8% per 1˚C drop in body temperature. A similar decrease in oxygen consumption and carbon dioxide production is observed. This decrease in metabolic rate arises from a global decrease in the rate of drug metabolism by the liver because the majority of the metabolic reactions in the liver are enzyme-mediated. The rate of these enzyme-mediated reactions is highly temperature sensitive; thus the rate of these reactions is significantly slowed during hypothermia. Hypothermia-induced reductions in clearance have been shown for a number of commonly used ICU sedatives such as propofol; opiates such as fentanyl and morphine; midazolam; neuromuscular blocking agents such as vecuronium and rocuronium; and other drugs such as phenytoin (Refer to Table 1). The specific alterations in drug metabolism and clearance will be further addressed in the upcoming sections of this chapter.

e. Gastrointestinal effects

Gastrointestinal (GI) motility decreases with mild hypothermia. In some cases, decreased motility leads to mild ileus which typically occurs at temperatures less than 32°C. Other physiological factors play a large role in the extent to which drugs and nutrients are absorbed across the gut wall. As with drug excretion in the kidney, drug absorption across the intestinal membranes depends primarily on passive diffusion with significant

contribution by active transport mechanisms for some drugs. Also similar to the kidney, cooling was shown to affect active drug transport via the ABCB1 transporter, more commonly known as P-glycoprotein, *in vitro*. However, no affect of cooling has been reported on passive diffusion, thereby, suggesting that passive processes are unaltered and active drug transport may be impaired during cooling. Further physiological factors that affect absorption include the pH of various biological compartments and the blood flow at the site of absorption. The physiochemical properties of the drug, such as its pKa and lipid solubility, in combination with the compartmental pH, will influence the extent of which the drug will distribute into a given compartment. It is expected that some drugs will have increased absorption while others may have decreased absorption during cooling depending on pH, lipophilicity, and primary site of GI absorption; however, no studies to date have thoroughly evaluated if these anticipated changes occur *in vivo* under mild hypothermic conditions. The effects of hypothermia on drug disposition and response will be further addressed in the next section.

ANALGESICS /SEDATIVE	**Primary Route of Elimination**	**Pathway(s) of Elimination**	**Volume of Distribution**	**Protein Binding**	**Half-life**
Fentanyl	Hepatic: 75%	CYP3A4	4 - 6 L/kg	80-85%	3-12 hrs
Propofol	Hepatic: 90%	CYP2B6/UGT	60 L/kg	95-99%	30-60 mins
Dexmedetomidine	Hepatic: 95%	CYP2A6	118 - 152 L/kg	94%	2-2.67 hrs
Remifentanil	Hepatic: 90%	Metabolized by esterases in blood and tissue	0.35 L/kg	92%	3-10 mins
Midazolam	Hepatic: 63 - 80%	CYP3A4	1 - 3.1 L/kg	95%	1.8-6.4 hrs
Lorazepam	Hepatic: 88%	Conjugation	1.3 L/kg	91%	9-19 hrs
Ketamine	Hepatic	CYP3A4 (major), CYP2B6 & CYP2C9 (minor)	2 - 3 L/kg	47%	2-3 hrs
Morphine	Hepatic: 90%	UGT2B7, CYP2C, CYP3A4	1 - 4.7 L/kg	30-40%	2-3 hrs
PARALYTICS					
Vecuronium	Bile: 30 – 50% Renal: 3 – 35% Hepatic: 15%	CYP3A4	0.2 - 0.4 L/kg	60 - 80%	51-80 mins
Rocuronium	Bile: Extensive Renal: 33% Hepatic: Minimal	CYP2D6/Renal	0.25 L/kg	30%	84-131 mins
Pancuronium	Renal: 50 – 70% Hepatic: 15% Bile: 5 – 10%	Renal elimination & Bile	0.19 L/kg	77-91%	1.5-2.7 hrs
ANTI-ARRYTHMICS					
Lidocaine	Hepatic: 90%	CYP1A2 (major), CYP3A4 (minor)	1.5 L/kg	60-80%	1.5–2.0 hrs

ANALGESICS /SEDATIVE	Primary Route of Elimination	Pathway(s) of Elimination	Volume of Distribution	Protein Binding	Half-life
Amiodarone	Hepatic: Extensive	CYP3A4, CYP2C8	60 L/kg	33-65%	15-142 days
Digoxin	Renal: 55 – 80% Bile: 6 – 8%	glomerular filtration, PGP Transporter	4 - 7 L/kg	25%	36-48 hrs
Diltiazem	Hepatic: Extensive	CYP450s	3 - 13 L/kg	77-93%	3-6.6 hrs
ANTI-HYPERTENSIVE					
Verapamil	Hepatic: 65 – 80%	CYP3A4, CYP2C9/19; PGP Transporter	3.8 L/kg	90%	3-7 hrs
Enalapril	Hepatic: 60 - 70%	Hydrolyzed in liver, OATP/MRP2 Transporter	0.2 – 0.4 L/kg	50-60%	11 hrs
Metoprolol	Hepatic: 95%	CYP2D6	5.6 L/kg	15%	3-7 hrs
Valsartan	Feces: 83% Hepatic: 7-13%	Primarily excreted as unchanged drug; OATP/MRP2 Transporter	17 L/kg	95%	6 hrs
Pressors and Iontropes					
Epinephrine	Hepatic & other tissues	Metabolized by MAO & COMT	N/D	N/D	2 mins
Norepinephrine	Hepatic & other tissues	Metabolized by MAO & COMT	N/D	N/D	2 mins
Phenylephrine	GI Tract: Extensive	Metabolized by MAO & sulfotransferase	40 L/kg	N/D	2-3 hrs
Milrinone	Renal: 80 - 85%	Primarily excreted as unchanged drug; Active tubular secretion	0.3 - 0.47 L/kg	70%	1-3 hrs
Dopamine	Hepatic: 80%	Metabolized by MAO & COMT	1.8 - 2.5 L/kg	N/D	9 mins
Vasopressin	Hepatic and Renal: Extensive	Metabolized by vasopressinases	N/D	N/D	10-20 mins
ANTI-CONVULSANT					
Phenytoin	Hepatic: Extensive	CYP2C9, CYP2C19; UGT Transporter	0.5 - 1.0 L/kg	90%	7-42 hrs
Phenobarbital	Hepatic	CYP2C9; UGT Transporter	0.5 – 1.9 L/kg	20-45%	2–7 days
Carbamazepine	Hepatic: 72% Feces: 28%	CYP3A4, CYP2C9; PGP/UGT Transporters	0.8 - 2 L/kg	76%	25-65 hrs
Keppra	Renal: 66% Hepatic: minimal	Primarily excreted as unchanged drug; some enzymatic hydrolysis	0.7 L/kg	< 10%	6-8 hrs

ANALGESICS /SEDATIVE	Primary Route of Elimination	Pathway(s) of Elimination	Volume of Distribution	Protein Binding	Half-life
ANTI-PLATELET/ CLOTTING					
Warfarin	Hepatic: 92%	Primarily CYP2C9 but also CYP2C19, CYP1A2, CYP2C8 & CYP3A4	0.14 L/kg	99.5%	20-60 hrs
Heparin	Hepatic	Metabolized by heparinise; cleared via reticuloendothelial system	0.07 L/kg	N/D	1-2 hrs
Dalteparin	Hepatic: extensive	Primarily by desulfation and depolymerization	0.04 – 0.06 L/kg	Low	3-5 hrs
Aspirin	Hepatic	Hydrolyzed by esterases in the liver to active metabolite	0.15 L/kg	50-80%	4.7-9 hrs
Clopidogrel	Hepatic: Extensive	CYP2C19, CYP3A4, CYP1A2 and esterases		98%	6 hrs
Rivaroxaban	Hepatic: Extensive Renal: 36%	CYP3A4/5 & CYP2J2	50 L/kg	92-95%	5-9 hrs
Dabigatran	Hepatic: 80%	esterases and glucuronidation	50-70 L/kg	35%	12-17 hrs
MISCELLANEOUS					
Quetiapine	Hepatic: 70 - 73%	CYP3A4	6 - 14 L/kg	83%	6 hrs
Haloperidol	Hepatic: 50-60% Feces: 15%	Glucuronidation; CYP3A4	9.5 - 21.7 L/kg	90%	18 hrs
Gentamicin	Renal: 80 - 100%	glomerular filtration	0.2 - 0.3 L/kg	<30%	1.5-3 hrs
Piperacillin / Tazobactam	Renal: 70 - 90%	glomerular filtration and tubular secretion	0.18 - 0.3 L/kg	16%	36-80 mins
Vancomycin	Renal: 40 - 100%	glomerular filtration	0.2 - 1.25 L/kg	30-55%	4 – 6 hrs
Pravastatin	Hepatic: Extensive	Extensive first pass extraction by the liver	0.46 L/kg	43-55%	2.6-3.2 hrs
Pantoprazole	Hepatic: 71% Feces: 18%	CYP2C19/CYP3A4	11 - 24 L/kg	98%	1 hr
Famotidine	Renal: 25 - 70%	glomerular filtration and tubular secretion	1 L/kg	15-20%	8-12 hrs
Corticosteroids	Hepatic	CYP3A4	Varies	Varies	Varies

Abbreviations: N/D: not determined; mins: minutes; hrs: hours; PGP: P-glycoprotein; UGT: UDP-galactose transporter; MAO: monoamine oxydase; COMT: catechol-O-methyltransferase; OATP: organic anion transporter; MRP2: Multidrug resistance protein 2.

Table 1. Pharmacokinetic characteristics of commonly used medications in critically ill patients

3. The effects of therapeutic hypothermia on drug pharmacokinetics

In general, hypothermia can affect drug disposition in various ways. We have previously discussed the physiological changes induced by hypothermia. These effects generally include decreases in active transport processes of drug absorption and excretion, no alteration in passive processes of drug disposition, and a general reduction in the overall rate of drug metabolism. Although these are general alterations, it is important to note that each of these alterations have been shown to be drug specific and requires particular evaluations of drug disposition in the cooled patient. In addition, hypothermia is also known to alter the different phases of drug pharmacokinetics. These phases can be broken up into absorption, distribution, metabolism and transport, and excretion. This section will highlight the effect of therapeutic hypothermia on each of these four phases, and the current research in the area. A summary of the current clinical studies on drug disposition is given in Table 2. In addition, Figure 1 summarizes the known physiologic and drug disposition effects of hypothermia and provides a statement of the level of evidence that currently exists in the published literature.

a. Drug absorption effects

Most drugs in the ICU are administered intravenously. However, some drugs are given non-intravenously, typically via oral administration. Drugs that are administered orally are subject to many factors that influence the rate and amount of drug that can be absorbed before it reaches the bloodstream. Some of these factors, such as disintegration and dissolution, are drug dependent and will vary among drugs based on their dosage form (tablet, capsule, etc) as well as the components that make up the drug (active ingredient, excipients, etc). Physiochemical properties of the drug, such as the pKa, lipophilicity, and solubility, will also influence the total amount of drug absorbed.

As previously addressed in the physiology section, gastrointestinal motility is known to decrease with mild hypothermia. Furthermore, a decrease in temperature can decrease blood flow at the site of absorption, and increase or decrease the gastric and duodenal pH, all factors that will ultimately affect a drug's absorption.

Pre-clinical studies investigated the effects of moderate hypothermia on these physiological factors. Hypothermia is associated with a decrease in passive transport via ABCB1. Results demonstrated a 30-44% decrease in the absorption rate constant, k_a, of pentobarbital, levodopa and uracil. However, these pre-clinical studies induced moderate or severe hypothermia. Therefore, the decrease in drug absorption may be more pronounced than what would be observed clinically under mild hypothermia.

Overall, the effect of hypothermia on drug absorption may lead to a decreased rate and prolonged time to reach maximal concentration for some drugs. Furthermore, the time of onset may be delayed and the magnitude of the pharmacological response, due to these reduced concentrations, may be diminished. However, current studies do not accurately reflect the range of temperature cooling *in vivo* and further clinical studies need to be done to determine if the magnitude of alterations in drug absorption is clinical relevant.

Study Group	Subject Population/ Temperature Cooled	Drug	Route of Elimination	Concentration & PK Parameters
Preclinical Studies				
Tortorici *et al*. [26]	CA rats/30˚C	Chlorzoxazone	CYP2E1	↓CLs, $t_{1/2}$, k_e. ↑V_d
Koren *et al.* [45]	Piglets/31.6˚C	Fentanyl	CYP3A4	↑Plasma concentrations, ↓CLs, ↓V_d, ↑half-life,
Bansinath M. *et al*. [38]	Dog/30˚C	Morphine	UGT, CYP2C, CYP3A4	↑Plasma concentrations, ↓CL 70%,$t_{1/2\beta}$ ↑2-fold, V_d ↓
Satas S. *et al*. [40]	Hypoxia newborn pig/35°C	Gentamicin	Renal Filtration	No change in CL
Nishida K. *et al*. [19]	Rats/32°C	PSP	Renal Tubular Secretion	Total CL ↓42%, plasma AUC ↑2-fold, renal secretion ↓
Jin J *et al*. [39]	In vitro kidney epithelial cell/32˚C	Digoxin	Renal Filtration	Direction from B to A ↓ 50%
Clinical Studies				
Fukuoka N. *et al*. [32]	TBI Patients/32-34˚C	Midazolam	CYP3A4	Plasma concentration↑, V_d↑ 83%, CL↓, K_e↓
Beaufort A. M. *et al*. [46]	Neurosurgical Patients/30.4˚C	Rocuronium	CYP2D6/Renal	CL ↓to 51%
Roka A. *et al*. [37]	HIE Infants/33-34˚C	Morphine	UGT, CYP2C, CYP3A4	CL ↓
Hostler D. *et al*. [33]	Healthy volunteers/35.5-36.5°C	Midazolam	CYP3A4	CL ↓11% per degree
Iida Y. *et al*. [25]	Brain Damage Patients/34°C	Phenytoin	CYP2C9 & CYP2C19	AUC ↑180%, CL ↓67% and K_e ↓50%
Liu X. *et al*. [20]	HIE Infants/33.5°C	Gentamicin	Renal Filtration	No change in CL
Caldwell J. E. *et al*. [35]	Volunteers/<35, 35-35.9,36-36.9°C	Vecuronium	CYP450s	CL ↓11.3% per degree

Abbreviations: CL: Systemic clearance; AUC: Area under curve; Ke: Elimination rate; Vd: Volume of distribution; T1/2: Half- life.

Table 2. Summary of the findings of clinical studies evaluating the effects of therapeutic hypothermia on drug disposition.

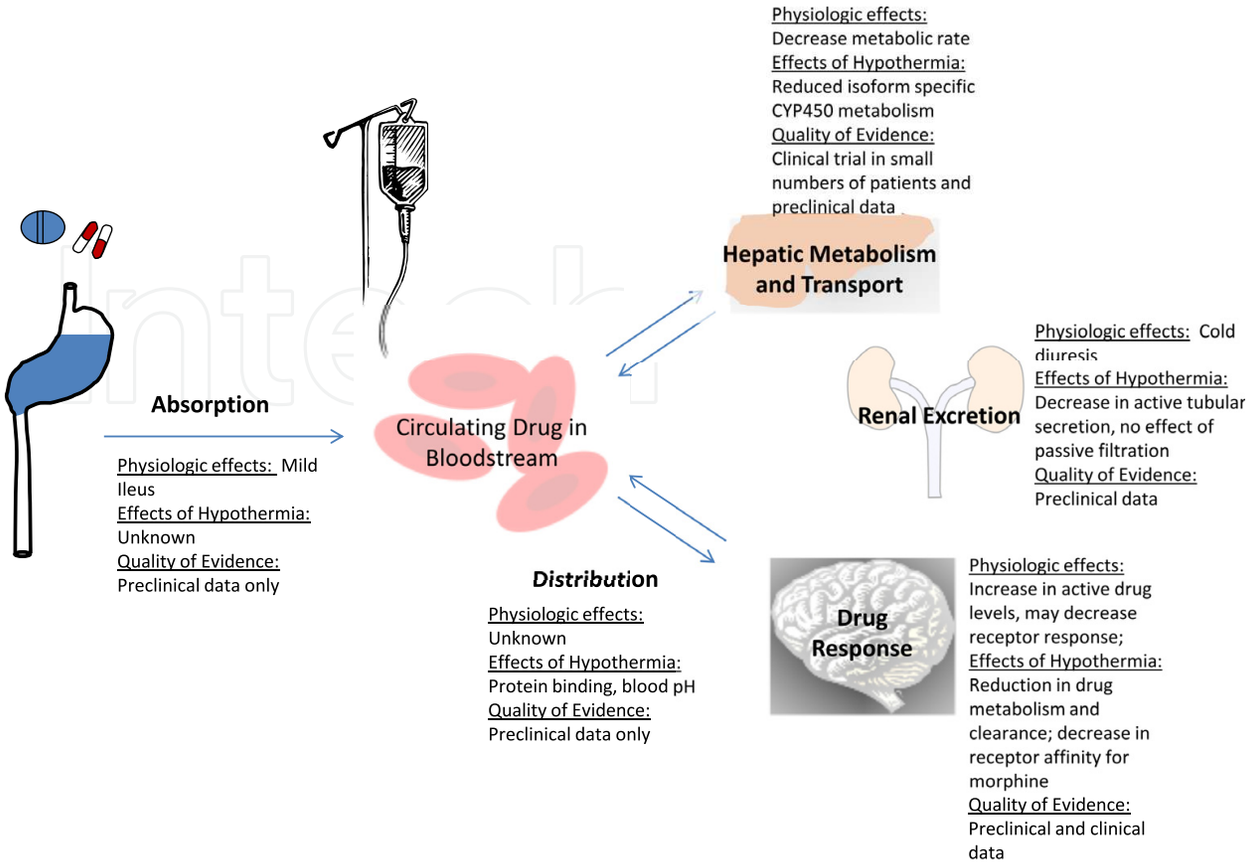

Figure 1. This figure depicts the known effects of therapeutic hypothermia on drug abosrption, distribution, metabolism, excretion and response. Also depicted is the quality of the current data with respect to each of these processes.

b. Drug distribution effects

When a drug is absorbed into the bloodstream, it distributes throughout the body into various tissues and organs. Generally, the space that the drug distributes into the body, or the volume of distribution (V_d), is important for drug dosing since it affects important pharmacokinetic parameters such as the loading dose and the half-life ($t_{1/2}$) of the drug. The factors that influence drug distribution include protein binding, blood pH and lipophilicity. As previously stated, many of the drugs used in the ICU have relatively large volumes of distribution (Table 1), which implies that the drug compounds preferentially distribute into the tissues over the blood. With drugs that have large volumes of distribution it is common for this distribution to first occur into the easily perfused tissues, followed by a more delayed distribution into more difficult to perfuse tissues.

Much of the effect of hypothermia on plasma protein binding is still largely unknown. Two *in vivo* studies (chlorzoxazone in rats and phenytoin in humans) showed unchanged plasma protein binding during hypothermia, whereas *in vitro* studies of sulfanilamide and lidocaine did show changes in the plasma protein binding. Sulfanilamide showed a 65% increase in plasma protein binding when cooled to 17°C while lidocaine showed a 24% decrease in plasma protein binding when cooled to 24°C. A possible explanation for the discrepancy

between *in vitro* and *in vivo* results could be the difference in cooling temperature. The *in vitro* studies cool to a much lower temperature than is possible *in vivo* (17˚C and 24˚C versus 31˚C) and therefore may demonstrate a greater change in protein binding. To date, studies have not reported altered protein binding over the mild therapeutic hypothermia temperature range.

Another factor that is influenced by hypothermia is the pH of the blood. As temperature decreases, the partial pressure of carbon dioxide decreases and the pH increases. For every 10 degree change in temperature, the blood pH increases from 7.40 to 7.55. Depending on the pKa of the drug, more or less of the drug will be ionized after the shift in pH. Consequently, more or less of the drug will be able to pass through permeable membranes. Theroretically, drugs like Lidocaine (pKa 7.9) that have a pKa between 7 and 8 may be most susceptible by these slight changes in blood pH. *In vivo* cooling is usually no more than a 6 - 7˚C change. Thus, blood pH would be expected to change in small increments and the clinical effects of these changes remain to be elucidated.

Finally, hypothermia may alter the lipid solubility and tissue binding of drugs. Preliminary studies demonstrate that hypothermia induced a decrease in transfer processes in water/n-octanol systems of atenolol and pindolol. Furthermore, phenytoin was shown to have increased tissue binding in rats at higher temperatures potentially due to temperature-mediated changes in protein conformation, leading to an altered tissue binding capacity.

Although hypothermia has been shown to have mixed effects on protein binding, blood pH, and lipophilicity at moderate to severe hypothermia, more studies are needed to determine the clinical magnitude and effects during mild hypothermia in patients. A change in any of these factors during mild hypothermia has the potential to alter the V_d of the drug. The limited number of published studies to date suggest no significant alteration in drug disposition during mild cooling, however, only a small number of drugs have been evaluated with respect to changes in distribution.

c. Hepatic drug metabolism

Many drugs that are administered to critically ill patients undergo extensive hepatic metabolism. These drugs are predominately metabolized by cytochrome P (CYP) enzymes. Various isoforms of the CYP450 enzyme family are involved in metabolism to varying degrees. These isoforms include CYP3A, CYP2C9 and CYP2C19, CYP2D6, and CYP2E1. Of these isoforms, CYP3A is one of the most important in hepatic drug metabolism in part due to its broad substrate specificity which allows for it to metabolize a wide range of compounds. Drugs commonly used in the ICU that are metabolized by CYP3A include midazolam, fentanyl, lidocaine, and vecuronium.

Midazolam is a well-known CYP3A4 substrate that has been most extensively studied in therapeutic hypothermia. One clinical study looked at the effect of cooling on midazolam pharmacokinetics in patients with TBI. The normothermic group achieved a steady state concentration of midazolam which was maintained during the 216 hours. Conversely, the

hypothermic group never reached a steady state concentration and midazolam concentrations were about five-fold higher than the normothermic group. Further studies by Hostler *et al.* also saw a reduction in the clearance of midazolam during hypothermia. In this study normal, healthy volunteers were infused with cold saline and plasma samples were obtained to determine midazolam levels and clearance. A significant difference was observed in the overall metabolism of midazolam under mild hypothermic conditions. Furthermore, this study determined that midazolam clearance is reduced by 11% per degree Celsius change in temperature. Similarly, another preclinical study reported about a 17% decrease in midazolam clearance at steady state in hypothermic rats versus normothermic rats after cardiac arrest.

Vecuronium, which is given as a muscle relaxant in the ICU, is another CYP3A4 substrate. The effect of hypothermia on vecuronium was studied in healthy human volunteers. Similarly to midazolam, the clearance of vecuronium was also decreased during cooling. Similarly, these studies demonstrated that an 11% reduction in vecuronium clearance is observed per degree Celsius change in body temperature. Furthermore, a preclinical study by Zhou *et al* demonstrated that hypothermia alters CYP3A activity, however the significant changes in CYP450 activity were isoform specific with significant alterations in CYP3A and CYP2E1 with no significant alteration in CYP2D or CYP2C probe metabolism. Collectively, these studies indicate that drugs which rely on CYP3A metabolism have decreased clearance during mild hypothermia, however, the reduced P450 activity appears to be isoform and potentially drug specific.

In addition to CYP450 enzymes, Phase II enzymes also play an important role in the metabolism of many drugs used in critical care. Phase II enzymes include UDP-glucuronosyltransferases (UGT), glutathione S-transferases, methyltransferases, sulfotransferases, and N-acetyltransferases. Of these enzymes, UGT is one of the only studied phase II enzymes and metabolizes a large number of drugs given in the ICU, such as morphine, propofol, phenobarbital, propranolol, aspirin, and acetaminophen. Of these, the effects of hypothermia on morphine have been most extensively studied.

Morphine, a commonly administered analgesic in the ICU, is predominately metabolized by UGT2B7 with almost no metabolism by Phase I enzymes. One study measured morphine concentrations in neonates with hypoxic-ischemic encephalopathy (HIE). This randomized study compared peak serum morphine concentrations in neonates with HIE who were randomly assigned to either a hypothermic or normothermic group. After 72 hours, six of the seven neonates in the hypothermic group had morphine concentrations greater than 300 ng/mL compared to one of six neonates in the normothermic group. Further, the clearance of morphine in the hypothermic group was significantly decreased. As previously mentioned, neonates undergo a longer, 72 hour duration of cooling. A pre-clinical animal study also showed a significant decrease in morphine clearance in the hypothermic model as compared to the normothermic model. These studies demonstrate a reduced clearance of midazolam during cooling. One possible explanation could be a decrease in UGT activity. Additional studies are needed on other UGT substrates to validate these results.

Digoxin is a calcium channel blocker used to treat arrhythmias in the ICU. A pre-clinical study of ABCB1 transport of digoxin showed that during mild hypothermia the rate of active transport was decreased. No difference in passive diffusion or tight junction activity was seen. The same group also studied the ABCB1-mediated transport of quinidine, another antiarrhythmic drug. In this study, no net effect was seen on quinidine transport during cooling. The authors propose that quinidine is also a substrate for the OATP transporter which may have influenced the results of temperature effects. Although these studies indicate that hypothermia may alter the active transport of drugs by ABCB1, further studies need to be completed to determine the *in vivo* relevance of these changes and explore the effects on other drug transporters.

To date, most of the clinical and pre-clinical studies demonstrate a decrease in hepatic metabolism particularly with the CYP enzyme system during therapeutic hypothermia. Although there is a general reduction in drug metabolism, the magnitude of these alterations appears to be pathway specific and therefore, not all hepatically eliminated drugs will have reduced metabolism. In addition, many of these current clinical studies are small and underpowered. Additional studies still need to be performed to determine the extent of hepatic metabolism on drug concentrations and how clinicians can best dose patients receiving therapeutic hypothermia.

d. Renal drug excretion

Renal drug elimination is a common route of elimination for hydrophilic drugs. Renal elimination can be divided into filtration, tubular secretion and reabsorption. Filtration is a passive process, whereas tubular secretion is an active process of renal elimination. To date, few clinical studies exist that investigate the effect of hypothermia on renal drug elimination. A small number of preclinical studies have explored how cooling affects renal filtration and secretion.

Gentamicin is a commonly administered drug in the ICU to treat infections, and predominately eliminated via passive filtration with little to no tubular secretion. Liu *et al.* showed that gentamicin concentrations remained unchanged in hypothermic neonates with HIE compared to normothermic neonates. This demonstrated that the clearance of gentamicin was not changed during mild hypothermia. Another study investigated the pharmacokinetics of gentamicin in piglets during mild hypothermia. They observed no change in gentamicin pharmacokinetics in hypoxic piglets versus normothermic piglets. These combined gentamicin studies coupled with the aforementioned evidence indicating no alterations in creatinine clearance suggest that mild hypothermia does not affect the passive process of renal filtration.

In conclusion, these studies suggest that the passive processes of renal filtration are unaffected by mild hypothermia, whereas the active processes of renal tubular secretion may be decreased. However, these conclusions are based off of a single preclinical study in rats that investigated the active process of tubular secretion (previously discussed in renal physiology section). To accurately assess the effect of hypothermia on renal excretion, further studies in humans are needed.

4. The effects of therapeutic hypothermia on drug response

In addition to the effects of therapeutic hypothermia on drug disposition and pharmacokinetics, hypothermia has also been associated with changes in drug response. The remainder of this section addresses drugs based on their therapeutic class and the current research showing changes in drug response. A summary of the clinical effects of hypothermia on drug response is given in Table 3.

Study Group	Subject population/ Temperature Cooled	Drug	Drug Response & PD Estimates
Heier T. *et al*. [43]	Patients undergoing surgery/34.5°C	Vecuronium	↑Duration of Action PK mediated, ↑Recovery Time
Leslie K. *et al*. [44]	Healthy volunteers/34°C	Atracurium	↑Response, ↑Duration of Action PK mediated
Beaufort A.M. *et al*. [46]	Neurosurgical patients/30.4°C	Rocuronium	↑Duration of Action PK mediated
Liu M. *et al*. [42]	Children/ 34, 31°C	Isoflurane	↓Dose Requirement
Puig M.M. *et al*. [41]	Guinea pig ileum/30°C	Morphine	↓Affinity to receptor
Bansinath M. *et al*. [38]	Dog/30°C	Morphine	↑Hypotension incidence

Table 3. Summary of the findings of clinical studies evaluating the effects of therapeutic hypothermia on drug response.

Analgesics/Sedatives. Medications given for analgesia and sedation are largely hepatically metabolized and are one of the most commonly used class of drugs in the ICU. We previously mentioned in the drug metabolism section that morphine is one of the most extensively studied analgesics and undergoes predominately Phase II enzyme metabolism by UGT2B7. The effect of hypothermia on morphine response was evaluated in a dog model. In the hypothermic group, a significant decrease in mean arterial pressure was observed, whereas no change in mean arterial pressure was seen in the normothermic group. Another *in situ* study measured the potency of morphine in guinea pig ileum. This study saw a decrease in the affinity of morphine for its target μ-receptor when the temperature was decreased from 37°C to 30°C. In addition, this study reported an increase in morphine affinity for its receptor when the temperature was raised from 37°C to 40°C. This study indicates that during cooling, morphine affinity for the μ-receptor is decreased; therefore, it is likely that morphine receptor response would be reduced during hypothermia even though the concentrations of morphine are likely to be elevated due to reduced morphine clearance.

Another study evaluated the effect of hypothermia on the drug response to isoflurane in children. Liu *et al.* noted that the isoflurane requirement in children decreased by 5.1% per degree Celsius. Furthermore, the isoflurane minimum alveolar concentration values decreased from 1.69±0.14% to 1.22±0% at 37°C and 31°C, respectively. The pharmacokinetic properties of isoflurane were not evaluated in this study so the overall pharmacokinetic change relative to the drug response and dosage is not known so it is unclear if these alterations are due to altered pharmacokinetics or pharmacodynamics. Isoflurane is metabolized predominately by

CYP2E1 and preclinical studies have demonstrated reduced CYP2E1 activity in the rat model during hypothermia. Thus, it is reasonable to postulate that the effects on isoflurane are likely due to pharmacokinetics. Future studies should investigate whether a decrease in CYP2E1 activity is responsible for the decrease in isoflurane response.

Paralytics. Drug response for the neuromuscular blocking agent vecuronium has been studied during therapeutic hypothermia. Mild hypothermia increased the duration of action of the second infusion of vecuronium in patients undergoing elective surgery. Another study saw a similar increase in the duration of action of vecuronium in healthy volunteers during mild hypothermia. An increased duration of action was also seen in atracurium during mild hypothermia. In these studies the increase in duration of action was due to increase concentrations of the paralytics due to reduced drug clearance (i.e. pharmacokinetics). No alteration in the pharmacodynamic response was observed under hypothermic conditions. Therefore, unlike morphine response, it appears that the pharmacodynamic response to paralytics is not altered during mild hypothermia.

In summary, therapeutic hypothermia has been shown to affect the drug response of analgesics, sedatives, and paralytics. A reduction in drug metabolism and clearance may explain part of the response change particularly with paralytics. Conversely, a reduced affinity of morphine for the μ-receptor has been reported. Careful pharmacotherapeutic monitoring in the clinic during hypothermia treatment may be necessary to prevent a potential therapy-drug interaction caused by changes in both drug concentration and in drug response during cooling.

5. Prospectus and future directions

Therapeutic hypothermia has been shown to be a beneficial neuroprotective therapy in critical care. In addition to the benefits for therapeutic hypothermia, there are potential side effects that can also occur. The effect of hypothermia on drug metabolism and clearance can lead to elevations in drug concentrations. Recent studies have reported that the effect of hypothermia on drug metabolism and the degree of change can be specific for the metabolism and elimination route. A small number of studies have investigated the effect of hypothermia on drug response including analgesics, sedatives and paralytics. The effect on drug response may be due to pharmacokinetic and pharmacodynamics alterations during hypothermia.

However, the effect of therapeutic hypothermia on drug disposition and response is still significantly understudied. To date, little is still understood as to how therapeutic hypothermia affects the wide array of drugs administered to critically ill patients in the ICU. In order to safely use this therapy in patients, it is imperative that we further evaluate the potential alterations on drug metabolism and response. Larger clinical trials in humans are necessary before we can fully understand the effects of therapeutic hypothermia on drug pharmacokinetics. Ultimately by understanding the physiological effects of hypothermia, awareness of hypothermia's effect on drug pharmacokinetics, and learning the potential side effects, we will be able to more safely and effectively use this neuroprotective strategy in a wide range of critically ill patients.

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