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The Impact of Hypothermia on the Pharmacokinetics of Drugs Used in Neonates and Young Infants

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Abstract: Therapeutic hypothermia (HT) is frequently used in neonates with hypoxic-ischemic encephalopathy and young infants during cardiopulmonary bypass (CPB). Hypothermia and CPB result in physiological changes contributing to pharmacokinetic (PK) and pharmacodynamic (PD) changes. Changes in the absorption, the volume of distribution (Vd) and the total body clearance (CL) of drugs used during hypothermia and CPB might lead to the interindividual PK variability resulting in either insufficient or toxic plasma concentrations and have an impact on the biodisposition and action of drugs. Both under- or overdosing of medicines in these critically ill patients may contribute to a worse overall outcome. Overall, hypothermia decreases CL but may decrease or increase Vd by changing intravascular blood volume, organ perfusion and enzymatic metabolic processes. In addition, maturational as well as organ specific changes may occur during hypothermia superimposed on the underlying disease and/or procedures such as extracorporeal membrane oxygenation (ECMO) or CPB. This paper will provide an overview of variables and potential covariates (*e.g.*, asphyxia, sepsis, multiorgan dysfunction syndrome, cardiac arrest) determining the PK of frequently used drugs. In addition, the effects of hypothermia on individual drugs are described as well as alternative ways for future study designs such as the use of population PK-PD and opportunistic sampling. Ultimately, these investigations are warranted to obtain specific dosing nomograms of medicines for use in clinical practice and to improve the treatment results of this vulnerable group of pediatric patients.

Keywords: Hypothermia, pharmacokinetics, pharmacodynamics, pharmacogenomics, developmental pharmacology, absorption, distribution, metabolism, and excretion, neonates, infants, covariates, asphyxia, sepsis, multiorgan dysfunction syndrome, cardiac arrest.

INTRODUCTION

This manuscript summarizes the currently available data on the influence of hypothermia on the pharmacokinetics (PK) and pharmacodynamics (PD) of drugs used in neonates and young infants. In general, neonates and young infants are stratified according to postnatal age for the study and provision of drug therapy - newborn infants aged 1 month or less, infants between 1 and 24 months of age [1].

Definition of hypothermia. Hypothermia (HT) is defined is a fall in core temperature to 35 °C, and is classified into mild (33–35 °C) to moderate (32.2–35 °C), and severe hypothermia (usually being defined as 28, 27, or 26.7°C) [2]. Hypothermia can occur in a variety of conditions, both accidental as well as induced. The latter within the context of a medical procedure such as open heart surgery or following resuscitation.

Accidental hypothermia is mostly an acute and uncontrolled event accompanied by concomitant morbidity. Causes of accidental hypothermia are numerous with exposure and immersion being most prominent [2]. The incidence of accidental hypothermia is hardly systematically investigated while the in-hospital mortality of adults with moderate or severe accidental hypothermia is around 40% [2-4]. Exact numbers on the incidence and outcome of accidental hypothermia among critically ill neonates and young infants are not available in the literature. There are several case reports and case series that report mortality ranging from 20-100% [5]. Accidental hypothermia in combination with trauma or sepsis is associated with a worse outcome [6-8]. Sepsis and trauma result in disturbed homeostasis and depletion of energy stores. The combination of shock combined with hypothermia may lead to a dramatic decrease in ATP production at the cellular level with increasing mortality [9-11]. In adult trauma patients accidental hypothermia in combination with coagulopathy and acidosis is an independent risk factor for mortality. Although both physiological and pharmacological changes during the hypothermic and rewarming period may be substantial, pharmacological therapies are usually limited within this time frame. All these factors make it difficult to study and isolate the effects of subsequent PK changes in this setting.

Induced, so called therapeutic hypothermia, in neonatal intensive care units (NICUs) and operating theatres is more prolonged (24-72 hours) and both cooling and rewarming are tightly regulated and controlled. In these circumstances most patients receive multiple drugs for sedation, analgesia, hemodynamic modulation and treatment of underlying diseases. Changes in PK and PD due to prolonged hypothermia may affect all of these treatment modalities and, as a consequence, outcome. Therapeutic hypothermia has been widely used in CPB during circulatory arrest to reduce metabolic rate and protect organ function. PK and PD data are limited in these patients and the effects of hypothermia and CPB on PK and PD are difficult to differentiate. CPB incorporates various processes that influence the PK and PD of anesthetics and thus confound the effects of CPB itself. An extensive review addressing changes in PK and PD during CPB will has been published [12]. Therapeutic hypothermia in the ICU setting has obtained increasing interest in all age groups as therapeutic hypothermia is nowadays used for the prevention of secondary brain damage both in adults and children

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[13-17]. Induced (therapeutic) mild to moderate hypothermia (32-35°C) is the first therapy with proven efficacy for post-ischemic neurological injury [13-15, 18-23]. Therapeutic hypothermia in neonates was already instituted since December 2006 following completion of the recruitment phase of the Whole Body Hypothermia Trial (TOBY) [21]. Worldwide two therapeutic hypothermia protocols after asphyxia are used. Either head cooling, or whole body cooling (WBC) is used to achieve the target cerebral temperature (33-34 °C) for about 72 hours as soon as possible (*i.e*. before 6 hours of life). Successful rewarming (to 37.0±0.2 °C over 6-12 hours, increasing by 0.5 °C per hour) and prevention of hyperthermia is an important factor in these protocols [24]. At this moment different pharmacological interventions in combination with hypothermia are explored to further improve neurological outcome in both neonates and adults [25-28]. Other clinical applications of therapeutic hypothermia include prevention of secondary neurological damage in young infants after CPR. Updated guidelines reflect new global resuscitation science and treatment recommendations derived from the 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care with Treatment Recommendations (CoSTR) conference, and The Hypothermia After Cardiac Arrest Study Group [29] to improve the neurologic outcome after cardiac arrest [17, 30-34], and/or traumatic brain injury [35-39] and rarely to be initiated in critically ill patients with metabolic encephalopathy [40-43]. Although the routine use of therapeutic hypothermia is still under debate in the pediatric setting, several studies have shown its feasibility [15-17, 32, 44, 45]. Furthermore, several recently published studies described induced hypothermia with ECMO or hypothermia in relation with CPB [46-50]. The use of combining hypothermia with ECMO has recently been extensively reviewed [51]. Based on the available literature the International Liaison Committee on Resuscitation [29, 52] recommends therapeutic hypothermia in infants and children who remain comatose following resuscitation of cardiac arrest. Recently Shah *et al*. conducted a systematic review and meta-analysis of clinical trials highlighting the role of therapeutic hypothermia in asphyxiated newborns and its positive effects [53]. Unfortunately, the importance of altered pharmacokinetics during therapeutic hypothermia and rewarming are not indicated as future research directions. Results of the therapeutic hypothermia trials (randomized controlled trials-RCT, pilot studies) are based on primary outcome parameters and neurological follow up. However, none of the available studies has included a detailed PK and/ or PD analysis. In other words for the interpretation of the results of the trials the potential confounder of toxic or non-therapeutic drug levels cannot be answered in a systematic way.

In summary, the PK and PD of drugs used during hypothermia and rewarming is not well understood as physiological and pharmacological considerations were primarily described in experimental and clinical studies in adults.

There are only a few studies dealing with altered PK of drugs such as gentamicin, fentanyl, morphine, midazolam, phenobarbital, phenytoin, vecuronium and topiramate during hypothermia in neonates, young infants and older children and usually in small numbers [54-58]. Currently there is a lack of information of alterations in drug concentrations and responses in the different age groups during hypothermia as well as a limited understanding of the specific mechanisms that result in changes in PK and PD.

THE IMPACT OF COVARIATES ON PHARMACOKINETICS UNDER HYPOTHERMIA: THE DISEASE-DEPENDENT PHARMACOLOGICAL CHANGES

The potential role of pathophysiological covariates (*e.g*., asphyxia, sepsis with multi-organ dysfunction syndrome, and cardiac arrest) on the pharmacokinetics of drugs used in neonates under hypothermia will be discussed here.

ASPHYXIA

Definition: Perinatal asphyxia (PA) is defined by the American Academy of Pediatrics (AAP) and the American College of Obstetricians and Gynecologists (ACOG). The incidence of hypoxic ischemic encephalopathy due to perinatal asphyxia is 2-9 per 1000 live term births. Although there are many advances in perinatal medicine the incidence of perinatal asphyxia has not fallen during the last decade, and is about 5.4 per 1000 live born neonates, respectively 1.8 per 1000 live births in neonates with hypoxic ischemic encephalopathy [59].

Pathophysiology: Perinatal asphyxia has been extensively reviewed in animals and neonates [60-62]. Brain injury secondary to hypoxic ischemic insult is the predominant form of all brain injuries in neonates [63-65] and results from perinatal hypoxic- ischemic and reperfusion injuries [66-70]. The cardiovascular response in the human fetus and neonate to perinatal asphyxia consists of cardiovascular dysfunction and a redistribution of the cardiac output [71], resulting in an increased blood flow to the brain, heart and adrenal glands with a decreased blood flow to the skin, small intestine, colon and kidneys [72]. Perinatal asphyxia results into delayed closure of the patent ductus arterious. However, usually it only delays the closure of the ductus, and, over time, the ductus typically closes without specific therapy. The prospective study by Martin-Ancel *et al*. has shown that impairment of one or more organs occurred in 82% of all neonates after perinatal asphyxia [73]. The brain was most often affected; 72% of all asphyxiated neonates suffered from hypoxic ischemic encephalopathy, renal dysfunction occurred in 42%, cardiac failure in 29%, and gastrointestinal dysfunction in 29% of all cases. Liver dysfunction in relation to asphyxia is documented both in experimental [74] as well as in clinical studies [75]. Epidemiologic data show that the incidence of acute kidney injury (AKI) is increased by about 47-61% and is of the non-oliguric type in 78 % cases and oliguric type in 22 % cases in severe asphyxia. Even though serum creatinine (SCr) - based AKI definitions are used as not ideal because SCr levels are dependent on the level of postmenstrual and postnatal age and limited by laboratory methods [76, 77]. Reduced glomerular filtration rate (GFR), low urine output and poor urea clearance (CL) in postmature asphyxiated infants was first described by McCance *et al*. [78]. AKI was shown to be an independent predictor of mortality in critically ill neonates. Compared with infants without AKI those with AKI have higher levels of urine biomarkers such as cystatin C and uromodulin but lower levels of epithelial growth factor [79].

Pharmakokinetics: As a consequence of pathophysiological changes during perinatal asphyxia hypoxic-ischemic events might result in changes of PK parameters. As already described earlier, perinatal asphyxia decreases the drug absorption and elimination by regional hypoperfusion whereas the drug distribution is larger compared to nonasphyxiated neonates: a.the glomerular filtration rate (GFR) in neonates is about 50 % less compared to neonates without asphyxia resulting in a decreased CL of renally excreted drugs (*e.g*., aminoglycosides) [1, 79, 80]. Serum gentamicin concentrations and SCr levels are increased in asphyxiated neonates but unaffected in asphyxiated neonates under hypothermia vs. normothermic asphyxiated neonates [54]. b. moderate and severe asphyxia is often associated with impaired hepatic function, which is likely to influence metabolism and CL of hepatically metabolized drugs such as sedatives, analgesics and anticonvulsants. For instance, the estimated morphine CL is lower and morphine plasma concentrations are higher [56], than is reported for non-asphyxiated infants as published by other authors [81-83]. The persistence and/or closure of a patent ductus arteriosus has a major impact on both the Vd and elimination of frequently used drugs in the preterm newborn especially, resulting in high interindividual PK variability [84-86], and summarized by Smits *et al*. [87].

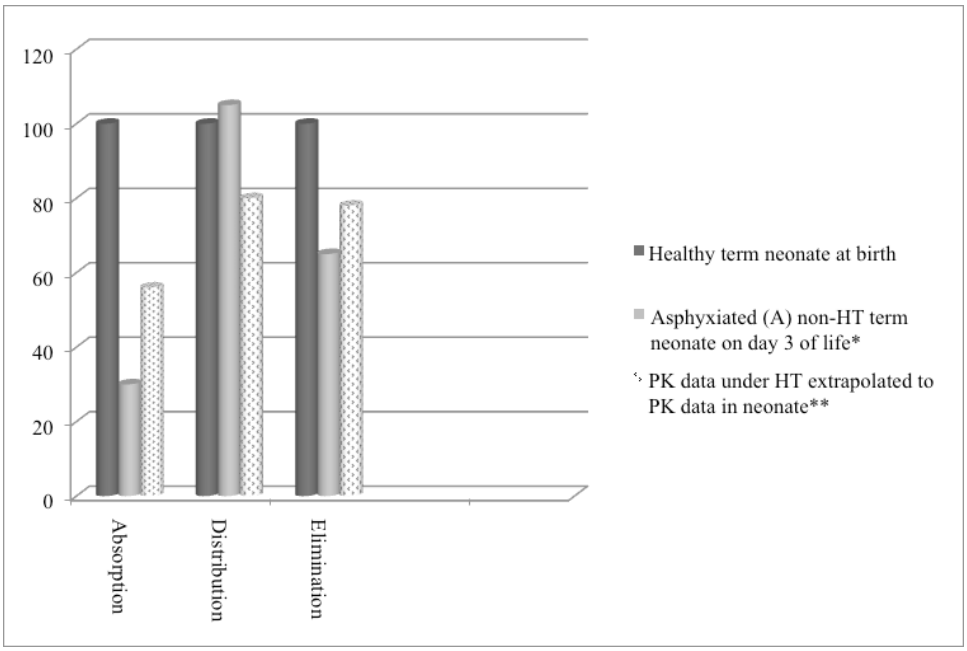

Fig. (1). Potential effects of asphyxia and hypothermia on drug disposition (absorption, distribution and elimination) in term neonates at birth and during the first week of life.

Legend: PK data are documented as a relative difference in PK parameters (Tmax, Vd, CL) between term non-asphyxiated neonates (the first column =100%) vs asphyxiated non-HT neonates on day 3 after birth (the second column), and under HT (the third column). PK parameters are documented as relative differences (%) in the absorption, the Vd and the total CL in HT group vs NT groups.

The effect of asphyxia on drug disposition results in a decreased rate of drug absorption and an altered elimination rate, whereas the volume of distribution is increasing. The effect of hypothermia on drug disposition results in a decreased rate of absorption (0-44%), changes in drug distribution (from by about 20% decreased rate to 25-83% increased rate), and in an altered total clearance (0-22%) in general [78, 104, 107,128].

*as reported by Kearns [110], and van den Anker [132], or ** by van den Broek [105].

SEPSIS AND MULTIORGAN DYSFUNCTION SYNDROME (MODS)

Definitions: In 2005, adult systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, septic shock, and multiorgan dysfunction syndrome (MODS) definitions were modified for neonates (age 0 days to 1 month), infants (age from 1 month to 2 year), children (from 2 year to 12 years) and adolescents and young adult (from 13 to 18 years). The goal of published criteria [88] was to facilitate the performance of successful clinical studies in children and neonates with sepsis and SIRS. An evidence-based approach to find the appropriate criteria for early onset sepsis (EOS) in the neonate is needed because of the low applicability of the definitions of SIRS and sepsis in neonates with culture proven EOS [89]. Validated organ function scores for children treated in the Pediatric Intensive Care Unit (PICU) [Pediatric Risk Mortality III, Pediatric Index of mortality 2, and Pediatric Logistic Organ Dysfunction] were suggested as the best available tools to estimate the severity of illness in critically ill children in literature.

Pathophysiology: According to recent data from the National Neonatal Perinatal Database (NNPD) in 2002, the incidence of neonatal sepsis has been reported to be 1-30 per 1000 intramural live births in tertiary care institutions. Early onset sepsis is a common cause of neonatal mortality [90] . If a sick neonate develops septic shock with cardiovascular dysfunction requiring fluid management and inotropic support renal failure occurs with an incidence of about 26% [91].

Pharmacokinetics: Sepsis and septic shock might, as dynamically changing conditions, influence drug absorption, distribution, metabolism and elimination resulting in changes of the key PK parameters: total body clearance (CL) and volume of distribution (Vd) of drugs. Antimicrobials used in neonates are primarily eliminated unchanged via the kidney or metabolized and eliminated via the liver. Correct dosing of antibiotics [92] is crucial to reach an optimal treatment outcome and requires a thorough knowledge of the PK of the different agents in critically ill septic infants, including septic neonates. In the literature a wide inter-individual and intra-individual variability in PK/PD of common studied aminoglycosides has been documented [93]. In critically ill adult patients enlarged and variable Vds were documented as a consequence of fluid management, capillary leakage and fluid retention. These changes [94] are significantly higher as compared to septic neonates who hypothetically have a larger Vd than adults. Circulatory failure and renal failure may result in variable CLs of drugs eliminated by the kidney or the liver. SIRS might be associated with downregulation of the expression and activity of cytochrome P450 enzymes involved in hepatic and intestinal drug metabolism [95]. Sepsis and septic shock dispose to inter-individual and intra-individual variability of PK parameters, which leads to challenges in predicting the PK of aminoglycosides in critically ill neonates, and consequently therapeutic drug monitoring (TDM) is recommended [96-98]. Disease-dependent PK changes identified as pathophysiological PK covariates based on evidence are shown in Table **1**. Although these covariates might modify PK of drugs used in neonates under hypothermia, their potential impact on PK under hypothermia is not well understood yet.

The Impact of Hypothermia on Pharmacokinetics (ADME): The Temperature-Dependent Pharmacological Changes

Physiological Changes Under Hypothermia

Hypothermia induces changes in physiological processes in many organ systems that may lead to PK and PD differences. Changes in Vd and CL will either result in ineffective or toxic plasma levels; both are potential detrimental and may worsen out-

Table 1. A summary of the currently known disease-dependent pharmacological (PK) changes under hypothermia in neonates and young infants (vs control groups).

PK - covariates	Absorption	Distribution	Elimination
Asphyxia	↓ or variable	NS or ↑*	↓
Sepsis	no data are available	↓or↑or variable	↓or↑or variable
MODS	no data are available	↓or↑or variable	↓or↑or variable
Cardiac arrest	no data are available	no data are available	no data are available

*in neonates with patent ductus arteriosus (PDA), NS not significant

come. Hypothermia increases systemic vascular resistance [99], decreases cardiac output [100] changes organ perfusion by redistribution of blood flow from the extremities, kidneys and liver [101, 102] to the brain and heart. Cerebral low blood flow and hypoperfusion of kidneys and splanchnic organs occurs in relation to the decrease in core temperature [103]. During rewarming cardiac output increases in neonates [100]. Rewarming introduces additional risks and challenges as the hypothermia-associated physiologic and pharmacologic changes are reversed. Thorensen *et al*. documented changes in heart rate and mean arterial blood pressure while others identified changes in cardiac output. These changes are reduced during whole body hypothermia and reach normal values at the end of passive rewarming [100, 104]. Table **2** summarizes the temperature-dependent physiological and PK changes for specific drugs used in neonates and young infants during hypothermia.

Pharmacological Changes During Hypothermia

ADME - absorption, distribution, metabolism and excretion (*i.e*, PK processes) is affected by developmental changes (*i.e.* maturational covariates), pathophysiological condition (*i.e.* pathophysiological covariates), therapeutic modalities (hypothermia, CPB, ECMO), and drug characteristics - drug formulations and differences in physiological factors (*e.g* blood and tissue pH, pKa) due to regional and systemic perfusion, the physical and chemical properties (*e.g*. ionization, lipid/water solubility) of individual drugs, plasma protein binding capacity, tissue binding capacity and metabolic processes. As a consequence changes in PK and PD occur [105-107]. A recent review summarizes the studies on changes in PK and PD during hypothermia in animals, adults and children [105].

Absorption

Pharmacokinetics: Drug absorption is most commonly characterized by the absorption rate constant (K_a) and the time to reach the maximum plasma concentration (t_{max}) that both can determine drug bioavailability (F), defined as the proportion of the dose that enters into the systemic circulation intact [108]. Drug absorption from the gastrointestinal tract can be influenced by drug formulation, drug´s physical and chemical properties, development (growth and maturation) and physiological pathways. Important developmental changes are age dependent changes in a number of gastrointestinal functions such as gastric acidity, gastric emptying, gut motility, gut surface area, secretion of bile acids and pancreatic lipases, gut drug-metabolizing enzymes and active transporters, first-pass metabolism, and diurnal variations [1, 109, 110]. Drug absorption [111] of the orally administered drugs, *e.g*., acetaminophen (paracetamol) is significantly reduced in the first week of life [111], and t_{max} of cisapride was prolonged in preterms as showed in one study [110]. When caffeine is administered orally, it is absorbed rapidly and nearly completely from the gastrointestinal tract as reviewed by Orozco-Gregorio *et al*. [112] similarly to orally administered antibiotics [113]. Developmental changes may be further influenced by several pathophysiological conditions. Asphyxiated neonates develop splanchnic hypoperfusion at the time of the hypoxic insult whereas the development of postasphyxiated seizures is associated with a significant impact on blood flow to the fetal gut that both might influence several of the above mentioned factors written by authors [114-116], [117], and [118, 119]. The impact of hypothermia or rewarming on splanchnic perfusion is not completely documented in neonates and young infants compared to adults [102, 120]. Plasma concentrations after oral administration are more variable than after the parenteral administration during hypothermia and the absorption was mildly delayed in hypothermic neonates compared to normothermic neonates due to the decreased drug absorption rate and the elimination [105].

Interpretation of PK data: a.the absorption is an age-dependent PK process and most drugs are absorbed generally slower in neonates and young infants compared to the older children [105, 121]. b. the effect of hypothermia on drug absorption results in a decreased rate in general (*i.e.* temperature-dependent changes by about 0 - 44% in $K_{a\ in}$ HT vs NT group) [105]. c. published clinical data are limited in hypothermic neonates and young infants therefore intrinsic (*e.g*. genotype, diseases) and extrinsic factors (*e.g*, comedication) must be considered to understand the developmental and temperature-dependent changes of the absorption. In this way the intra-/ interpatient PK variability of orally administered drugs, which seems to be high, can be identified. Age-, temperature- and disease-dependent changes on drug absorption are documented (Table **3**).

Distribution

Pharmacokinetics: Drug distribution represents drug diffusion from the circulating blood pool into tissues, organs, and other spaces of the body. Vd relates the drug concentration measured in plasma to the total amount of a specific drug in the body. Drug distribution can be influenced by drug´s physical and chemical properties, development (growth and maturation), physiological and pathophysiological conditions. However Vd indicates in part if drugs are confined to the plasma compartment, extracellular compartment or fatty tissues. Changes in body composition seen especially in neonates and infants can have a significant impact on the Vd. Developmental changes of distribution during the first year of postnatal life are shown in Table **4**. Vd of the central compartment is usually larger for drugs confined to the extracellular compartment whereas Vd of the peripheral compartment is relatively decreased or not affected for lipophilic drugs in neonates compared to adults. Drugs with a high protein binding may have significant changes in Vd as binding capacity is reduced in neonates and infants determined by low albumin/plasma concentration ratios. For drugs such as digoxin, The Vd is increased because of enhanced myocardial and erythrocyte binding in the neonatal population [122]. Furthermore intravascular distribution volume is decreased by hemoconcentration thereby influencing PK during hypothermia [123-125]. As described before redistribution of blood flow, hemoconcentration and reduced tissue perfusion will affect Vd for most drugs or Vd will remain unaltered [105] but data in neonates and infants are

Table 2. The temperature-dependent physiological and PK changes for specific drugs used in neonates and young infants during hypothermia (HT) vs normothermia (NT) groups, modified after Zanelli *et al*. [106].

Physiological changes during HT	Pharmacological changes during HT	PK parameters during HT	Cpl potentially related to PK during HT	Specific drug used as a model drug during HT
Cerebral flow↓	**Distribution ↓**	**Vd ↓** **Cpeak ↑**	**Cpl ↑**	a. *hydrophilic* drugs*:* *e.g*. antimicrobials -*AMGs, ampicillin* b. *lipophilic* drugs: *e.g*. anticonvulsants -*diazepam,* analgesics - *fentanyl*
Splanchnic flow ↓	**Absorption ↓** *or unchanged*	**AUC p.o.↓** **Ka↓, t_{max} ↑** **F ↓** (AUCp.o./AUC i.v.) *or unchanged*	**Cpl ↓** *or unchanged* *or variable*	*orally administered* drugs: *e.g*. anticonvulsants -*topiramate*, vasodilator agents - *sildenafil*
Blood volume ↓ **Extracellular water ↓↑**	**Distribution ↓** *or* **↓↑** *or unchanged*	**Vd ↓** *or* **↓↑** *or unaltered*	**Cpl ↑** *or* **↑↓** *or unaltered*	a. *hydrophilic* drugs: *e.g*. antimicrobials - *AMGs, ampicillin* b. *lipophilic* drugs: *e.g*. anticonvulsants -*diazepam,* analgesics - *fentanyl* cardiovascular drugs -*digoxin*
Liver flow ↓	**Elimination ↓** *or unchanged*	**CL ↓** **AUC ↑** **$T_{1/2}$ ↑**	**Cpl ↑** *or unchanged* *e.g*. high CL drugs Cpl ↑ *NS* *e.g.* low CL drugs	*a.high hepatic CL* drugs: *e.g*. analgesics - *morphine, fentanyl* b. *low hepatic CL* drugs: *e.g*. anticonvulsants - *diazepam, phenobarbital, phenytoin*
Metabolic capacity ↓	**Elimination ↓** *or unchanged*	**CL ↓** **AUC ↑** **$T_{1/2}$ ↑**	**Cpl ↑** *e.g*. l*ow* CL drugs **or Cpl ↑** *NS* *or unchanged* *e.g. high* CL drugs	a. *low hepatic CL* drugs: *e.g*. anticonvulsants - *diazepam, phenobarbital* *b.high hepatic CL* drugs: *e.g*. analgesics - *morphine, fentanyl*
Renal flow ↓	**Elimination ↓** **Excretion ↓**	**CL ↓** **AUC ↑** **$T_{1/2}$ ↑**	**Cpl ↑**	*a.renal CL* drugs: *e.g*. antimicrobials -*AMG, ceftazidime*, *a.renal CL (in)active metabolites:* *e.g*. sedative drugs - *midazolam, propofol,* miscellaneous - *theophylline*
Protein binding ↓ *or unaltered**	**Elimination ↓** or **unchanged**	**CL ↓** **$T_{1/2}$ ↑** **f_B ↑** *or f_B* *unchanged*	**Cpl ↑** *e.g high* protein binding) *or unchanged* *or* **Cpl↑** *NS* *e.g* l*ow* protein binding drugs	a.*high* protein binding drugs: anticonvulsants -*diazepam, valproic acid* b. *low* protein binding drugs *e.g. low* hepatic CL drugs - anticonvulsants *phenobarbital, phenytoin* *e.g. high* hepatic CL drugs -analgesics - *morphine, fentanyl, sufentanil*

(Table 2) Contd….

Physiological changes during HT	Pharmacological changes during HT	PK parameters during HT	Cpl potentially related to PK during HT	Specific drug used as a model drug during HT
Cardiac output ↓	**Absorption ↓** **Distribution ↓↑** **Elimination ↓** *or unchanged*	**Ka ↓** **AUC** p.o. **↓** **F ↓** **Vd ↓** or **↑↓** **CL ↓** **$T_{1/2}$ ↑** **f_B ↑** or **↑↓**	**Cpl ↓** *or* **Cpl ↑↓** *or variable* *or unchanged*	*All of previously reported drugs*

Table 3. Age-dependent (developmental) PK changes on drug absorption in neonates and young infants (vs adults): the impact of asphyxia (asphyxia vs non-asphyxia) and hypothermia (HT) versus normothermia (NT) on drug absorption [105, 121].

Age-dependent (developmental) changes [121]	Drug Absorption/bioavailability
Gastroesophageal reflux	variable/unpredictable
Gastric emptying and GI transit time	irregular < 6-8 months (shorter time: *e.g*., *theophylline*)
The capacity for gastric acid production	dynamically changing/ overall ↓ < 2 years (increasing: *e.g*., *penicillin, ampicillin*)
Drug absorption from the intestine, intestinal metabolism, gut surface	from ↓ or equal/variable or ↑
First-past uptake (liver, intestine)	↓ systemic bioavailability (*e.g*., *high hepatic extraction drugs*)
Gut flora	↓ < 16 months (*e.g*., *digoxin*)
Drug absorption from the rectum	↓ or ↑ or variable (*e.g*., *diazepam, valproic acid)*
Asphyxia	**↓ or variable, A vs non A**
Hypothermia [105]	**unaltered or ↓ (0-44%), HT vs NT**

still sparse. Moreover, changes in protein concentrations will affect unbound fractions of drugs.

Interpretation of PK data: a.the distribution of age-dependent PK processes is primarily related to developmental physiological changes and physiochemical properties of the drug. Vd is larger for hydrophilic drugs in neonates and young infants especially compared to adults. b. distribution of drugs is temperature - dependent and affected by factors as target temperature, and physiochemical properties (water/lipid solubility, tissue- and protein binding capacity) [105]. c. published clinical data are limited in hypothermic neonates and young infants. However, additional pathophysiological conditions (*e.g*. asphyxia, sepsis, PDA) may influence drug distribution. Age-, temperature- and disease-dependent changes on the drug distribution are summarized (Table **4**).

Elimination

Pharmacokinetics: The liver and kidney are the primary organs of drug metabolism and excretion (elimination). CL is a measure of drug elimination. Hepatic CL of unbound drugs can be interpreted as a measure of liver metabolizing activity. Drug metabolism is influenced by development, drug-metabolizing enzymes, hepatic flow, and protein binding. Hepatic CL by cytochrome P 450 - enzymes activity is highly age-dependent [126, 127]. Both cytochrome P450 as well as other oxidative enzymatic reactions are identified as a temperature dependent variable [105, 128]. Hepatic CL may be influenced by physiological parameters (hepatic blood flow) and characteristics of individual drugs (*e.g* protein binding capacity, hepatic extraction ratio). Hepatic CL of high hepatic extraction ratio- drugs seem to be altered more substantially due to lower hepatic flow than high extraction-ratio drugs. Renal CL is defined as renal excretion rate. Renal CL is influenced by renal flow, GFR and tubular function due to reabsorption and active secretion. The GFR is commonly estimated from serum creatinine in adults and children. Serum creatinine is an indirect measure of renal function and does not always reflects actual GFR, especially in neonates and infants during the first year of life [77, 129, 130]. Renal blood flow is also decreased during hypothermia at least in animal studies. Elimination of drugs by GFR will subsequently decrease. It is unclear whether tubular excretion and reabsorption is affected as well [105].

Table 4. Age-dependent (developmental) PK changes on drug distribution in neonates and young infants (vs adults): the impact of asphyxia (asphyxia vs non-asphyxia) and hypothermia (HT) versus normothermia (NT) on drug distribution [105, 108, 121].

Age-dependent (developmental) changes [108, 121]	**Drug Distribution**
Proportional body composition (based on body weight)	↑ Vd of the central compartment: *e.g., hydrophilic drugs)*
Proportional body composition (based on body weight)	not affected (Vd of the peripheral compartment*: e.g., lipophilic drugs*)
Drug binding capacity (plasma, tissue)	↓ ↓
Drug binding capacity (myocard)	↑ two-three times < 36 months (*e.g., digoxin*)
Drug binding capacity (erythrocytes)	↑ three times < 36 months (*e.g., digoxin*)
Albumin/plasma ratio	↓
Asphyxia	**NS or ↑** (*e.g., ceftazidime)* A vs nonA
Hypothermia [105]	**↑ (25-83%) or↓ (20%)** or unaltered, HT vs NT

Interpretation of PK data: a. drug metabolism is an age-dependent PK process primarily reflecting biotransformation leading to reduced or increased pharmacological action while development has a profound effect on the expression of CYP450 [1, 126]. Drug metabolic capacity is about 10% in neonates compared to adults of individual drugs[110]. b. drug excretion is determined by developmental changes of renal function and reaches adult values by early childhood. c. reduction of drug clearance during hypothermia can mainly be attributed to reduced activity of cytochrome P 450 [131] and physiological changes during HT. The total CL of high-CL drugs is especially dependent on the target temperature and more altered than the CL of low-CL drugs (by about 0 - 22%), whereas the rate of enzymatic conversion is age-, temperature and disease-dependent *(e.g. asphyxia*) and reduced in hypothermic neonates and young infants. Developmental changes and the impact of asphyxia and hypothermia on the drug elimination are summarized in Table **5**.

The Impact of Hypothermia on Pharmacokinetics Under Hypothermia: Specific Drug-Dependent Pharmacological Changes

A summary of the published clinical PK studies in neonates treated for hypoxic-ischemic encephalopathy (HIE) under hypothermia are shown in Table **6**. The primary PK parameters of orally administered drugs (*e.g., topiramate*) are not significantly different between deep (29.7 – 33.7 °C) vs mild (32.7-33.4°C) hypothermia, and between the dose-respecting groups in small number of investigated neonates whereas hypothermia resulted in higher drug Cpls [57, 105] and therefore changes in the documented secondary PK parameters [105] compared to normothermic neonates.

Potential effects of asphyxia and hypothermia on drug absorption, distribution (Vd), and elimination (CL) in neonates are shown in Fig. (**1**). PK data are very limited for drug absorption from the gastrointestinal tract. The impact of asphyxia on ceftazidime Vd was not significantly inreased in asphyxiated neonates vs non asphyxiated neonates (Vd=344 ±79 l/kg vs Vd=336±46 l/kg, p=*NS*), whereas ceftazidime CL was significantly reduced in asphyxiated neonates (Cl=60.8±8.3 ml/h/kg vs 40.9±6.1 ml/h/kg, p<0.001)[80, 132]. Overall effects of hypothermia on drug biodisposition is drug absorption, distribution and elimination is mentioned below [105, 106, 133]. Differences on drug disposition (ADME) are shown between adults, term non-asphyxiated neonates at birth and PK under hypothermia (Fig. **2**). Developmental changes in absorption are difficult to generalize [134] although the renal clerance (CL) was found to be significantly reduced at the birth [135-137]. The hepatic clerance as represented by metabolic capacity was reduced to 10% at the birth [110, 126, 138-146]. Developmental changes consists of changes in body composition related to changes in Vd. Schematically PK changes are shown related to the optimal dosage adjustment (Fig. **3**).

Cardiovascular Drugs (Dopamine, Dobutamine, Digoxin)

Drug specificity: Cardiovascular drugs are used for treatment of heart failure resulting from a variety of underlying conditions. Drugs widely used in neonates and young infants are selected inotropic agents (dopamine, dobutamine, epinephrine, norepinephrine), new inotropic agents (amrinone, milrinone), and preload- and afterload-reducing drugs (*e.g.* nitroprusside, captopril, enalapril) and occasionally digoxin.

The impact of development on PK: The impact of development on PK of cardiovascular drugs is poorly understood. Response of the immature heart to inotropic agents is limited in neonates and young infants compared to the effects in older children or adults [147-149]. Digoxin is a low protein bound drug (20 % to 30%), with a greater Vd compared to adults due to a high myocardial and erythrocyte binding. However renal excretion is lower compared to adults [122] . Dopamine and dobutamine are the most frequently

Table 5. Age-dependent (developmental) PK changes on drug elimination in neonates and young infants compared to adults: the impact of asphyxia (asphyxia vs non-asphyxia) and hypothermia (HT) *versus* normothermia (NT) on drug elimination [105, 126, 127, 130].

Age-dependent (developmental) changes [127, 130]	Drug Elimination
Renal clearance	↓
GFR (inulin clearance)	↓
GFR (enzymatic creatinine clearance)	↓
GFR (cystatin C clearance)	↓
Tubular excretion (*p*-aminohippuric acid)	↓
Hepatic clearance	↓
Bromsulphalein clearance	↓
Metabolic capacity – categories [**110**, **126**]	↓
Enzymes *expressed during the fetal period* but silenced or *low expressed* within 1-2 years after birth	*e.g*., CYP3A7. ADH1A: *alcohol*
Enzymes *expressed constantly* during fetal period but increased postnatally	*e.g*., CYP2C9: *phenytoin, propofol* *e.g*., CYP2C19: *benzodiazepines, proton pump inhibitors* *e.g*., CYP2D6: *codeine, beta-blockers, propaphenone*
Enzymes expressed in the third trimester and *substantial increased* in the first 1-2 years	*e.g*., CYP 3A4/5 *midazolam, cisapride* *e.g*., CYP1A2 *caffeine and theophylline* *e.g*., CYP2B6 *propofol* *e.g*., UGT2B7 *morphine*
Asphyxia	**↓ A vs nonA**
Hypothermia [105]	**↓ or unaltered (0-22%), HT vs NT**

Table 6. A summary of clinical PK studies previously reported in neonates treated for hypoxic-ischemic encephalopathy (HIE) and covariates under hypothermia: Primary and secondary PK parameters hypothermia (HT) versus normothermia (NT), [58, 105, 106].

Specific Drugs author/year	Target temperature (°C)	Investigated group	Primary PK parameters: Vd (L/kg) CL (L/kg/h)	Secondary PK parameters: Ka, F, AUC, $T_{1/2}$	Cpl_s HT vs NT (vs control groups)	Covariates of PK
Antimicrobials						
Gentamicin Liu *et al*./ 2009 [54]	33.0-34.0	neonates	not reported	not reported	↑CplGe≥2mg/l**NS* ↑CplGe (a Q 36-h vs a Q 24-h dosing interval under HT	sepsis HIE
Frymoyer *et al*./2013 [158]	33.5	neonates	CL↓	not reported	↑CplGe	sepsis HIE

(Table 6) Contd….

Specific Drugs author/year	Target temperature (°C)	Investigated group	Primary PK parameters: Vd (L/kg) CL (L/kg/h)	Secondary PK parameters: Ka, F, AUC, $T_{1/2}$	Cpl_s HT vs NT (vs control groups)	Covariates of PK
Frymoyer *et al.*/2013 [159]	33.5	neonates	CL↓	not reported	↑CplGe	sepsis HIE
Mark *et al.*/2013 [160]	33.5	neonates	CL↓	$T_{1/2}$↑		sepsis HIE
Neuroprotectives						
Phenobarbital Fillipi *et al.*/2011 [58]	33.0-34.0	neonates	Vd ↑ CL↓	AUC ↑ $T_{1/2}$↑	↑CplPhe	HIE Dopamine (limited data) HIE
van den Broek *et al.*/2013 [209]	33.0-34.0	neonates	no (clinically relevant) effect	no effect	no effect HT only	HIE
Shellhaas *et al.*/ 2013 [208]	34.5 (±0.5)	neonates	no effect	no effect	no effect	
Topiramate Fillipi *et al.*/2009 [57]	33.5	neonates	CL↓	AUC ↑	CplTPM↑	HIE
Phenytoin Bhagat *et al.*/2006 [205]	35.7	case report neonate	not reported	not reported	Cpls↑	anesthesia
Analgesics						
Morphine Róka *et al.*/2008 [56]	33.0-34.0	neonates	CL ↓	AUC↑	Cpls↑	HIE

******NS* no significant difference

Table 7. Drug - dependent PK changes: an impact of drug specificity on *aminoglycosides* (*e.g.*, *gentamicin*) biodisposition and action in neonates and young infants (vs adults).

Changes in Vd are:	II. Changes in CL are:
• Temperature-dependent • Age-dependent (body composition) ↑ • Drug-dependent (hydrophilic drug) ↑ • Disease-dependent (*e.g.* sepsis)	• Temperature-dependent • Age-dependent changes (renal excretion) ↓ • Disease-dependent (*e.g.* sepsis)

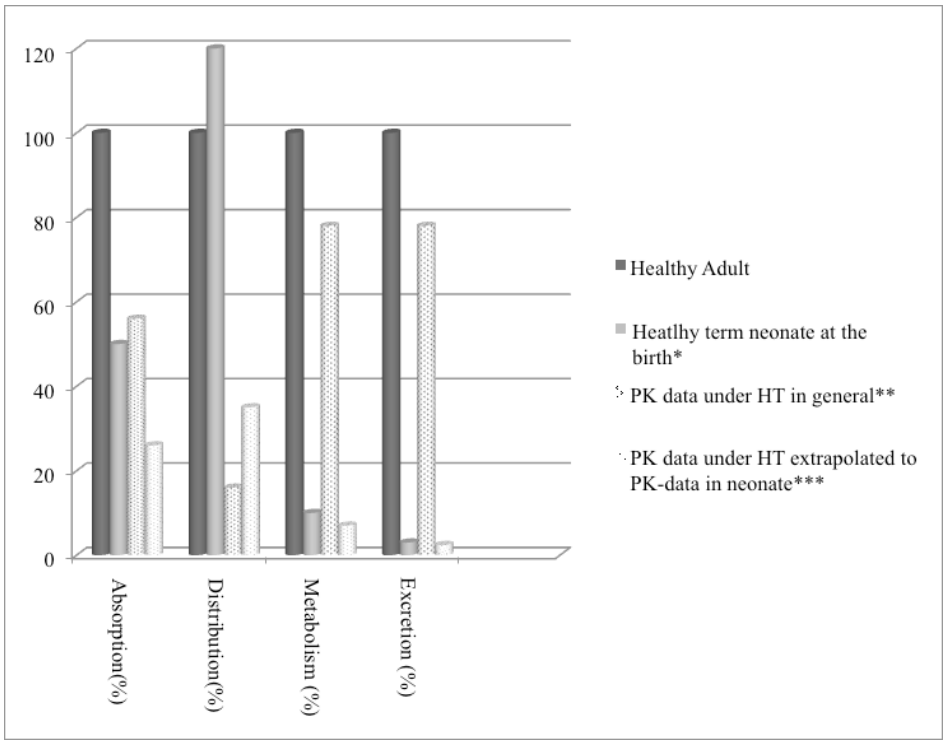

Fig. (2). Potential PK differences in drug disposition (absorption, distribution, metabolism and excretion) in adult, term neonate at birth and potential PK changes under hypothermia.

Legend: PK data are documented as relative differences in absorption, distribution, metabolism and excretion (ADME) between healthy adults (the first column=100% of the overall activity) and healthy term neonates (the second column=% of adult activity) at birth and during the first week of life. PK data under HT are documented as relative differences (the third column= a relative diference %) in hypothermia (HT) vs NT (normothermia) groups in general, and under hypothermia extrapolated to PK - data in neonates (the fourth column= a relative diference %). Drug disposition is described by PK parameters (Tmax, Ka, Vd and CL). Developmental PK data and renal clearance based on GFR are derived from the literature. Developmental changes in distribution were documented by extracellular water changes: 20% of body weight in adults compared to 45% of body weight in neonates with consequently changes in Vd.

The effect of hypothermia on drug disposition results in a decreased rate of absorption (0-44%), changes in drug distribution (from by about 20% decreased rate to 25-83% increased rate), and in an altered total clearance (0-22%) in general as documented in figure 1. This effect may represent that proportional decreased rate of absorption (from 26% to 45%), decreased rate of distribution (from 35% to 45%), metabolism (from 7% to 10%), and excretion (from 2.4 to 3.0%) of the overal activity 100 % under HT in term neonates at birth and during the first week of life [104,110,128].

*as reported by Kearns [110], and ** by van den Broek [105] or ***by other authors [104, 110, 128].

used inotropic agents in the neonatal population. Dopamine has a plasma half-life ($T_{1/2}$) of about 4-5 min in preterm neonates [150].

The impact of hypothermia on PK: Results of experimental and clinical studies under HT are based on pharmacodynamic outcome parameters. Hypoxia predisposes to elevated digoxin serum concentrations and digitalis intoxication because of decreased renal excretion [151]. There are no PK data available during hypothermia in neonates and young infants treated with vasopressors drugs.

Antimicrobial Drugs

Aminoglycosides (Gentamicin), (Table 7)

Drug specificity: Gentamicin is an aminoglycoside (*e.g*., amikacin, netilmicin, tobramycin), a bactericidal antibiotic, widely used for the treatment of neonatal sepsis due to gram-negative bacteria. Aminoglycosides are synergistic with β-lactam antibiotics in the treatment of group B streptococcal infections.

The impact of development on PK: Aminoglycosides are hydrophilic and therefore well distributed over extracellular fluids. The changes in Vd are dependent on age related changes in total body composition; Vd decreases over time to normal adult values. Aminoglycosides are eliminated via glomerular filtration, which is age dependent. Interindividual variability of PK does exist especially in the first week of life [152, 153].

The impact of hypothermia PK: During CPB and deep hypothermia (18-25°C) gentamicin Vd increased two fold, whereas Cl decreased. It is unclear if these effects reflect the influence of hypothermia or CPB [123-125, 154, 155]. Induced hypothermia to 29°C was associated with decreased Vd and Cl at least in pigs [133]. Mild hypothermia of 35°C however did not affect PK in juvenile pigs [156]. Liu *et al*. confirmed this finding in 55 neonates cooled to 33.0 - 34°C post asphyxia. Toxic serum trough concentrations were unaffected in hypothermic asphyxiated neonates vs. asphyxiated normothermic neonates without PK determination [54, 97, 157-160]. Aminoglycosides are drugs with a low therapeutic index and more stringent TDM is recommended in all neonates during hypothermia to prevent drug toxicity and to optimize drug efficacy.

Glycopeptides (*e.g*., Vancomycin, Teicoplanin)

Drug specificity: Vancomycin is a glycopeptide with a high water solubility (logP -3.1) and moderate protein binding (55%). This drug exerts a high renal clearance through glomerular filtration [161-164].

The impact of development on PK: No data are available on protein binding in neonates with the exception of teicoplanin with a documented protein binding to neonatal serum of 71.9-80.5%. [165, 166]. PK differences between adults, neonates and young infants show a larger Vd and low CL that results in higher PK variability in younger infants. *The impact of hypothermia on PK:* There are no

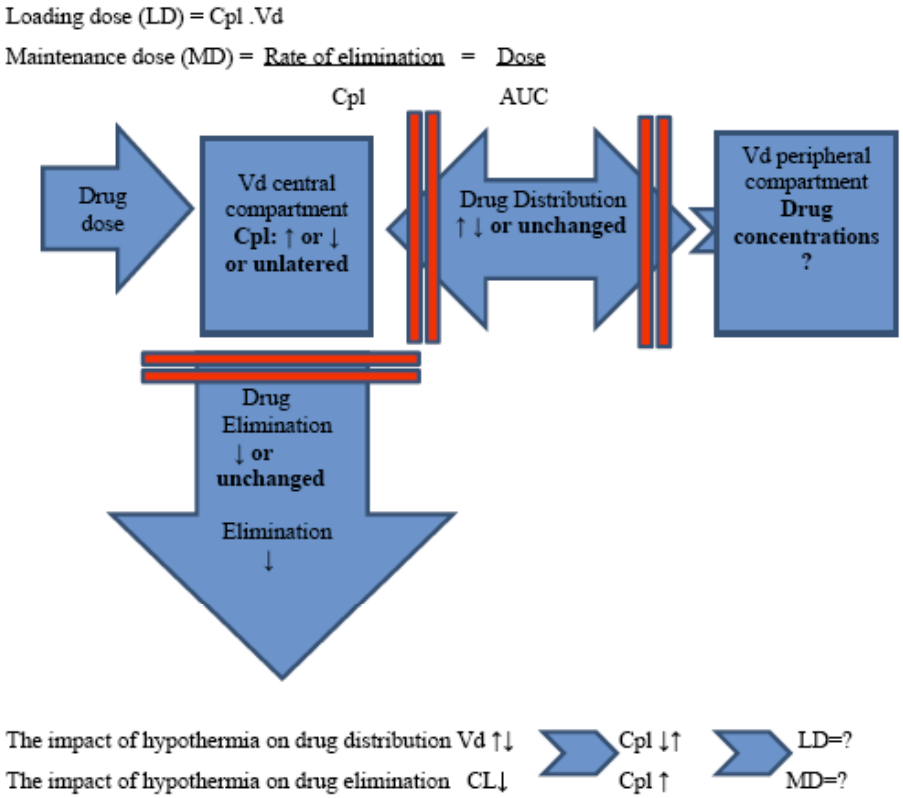

Fig. (3). Basic two -compartment model shows schematically drug distribution between the central and peripheral compartments [108] and drug elimination related to plasma concentration (Cpls) changes under normothermia , and under hypothermia (HT), [105].

trials assessing the effect of hypothermia on vancomycin CL. A decrease in renal perfusion will likely result in a decreased vancomycin CL. Especially in post cardiac arrest patients with a high risk of acute renal injury this could lead to toxic plasma levels. Based on the available literature vancomycin dosing intervals should be based on age and renal function. Vancomycin is a drug for which is TDM is recommended to adjust dosing.

Penicillins (*e.g.*, Ampicillin)

Drug specificity: Ampicillin is an antibiotic widely used in the treatment of neonatal sepsis due to susceptible strains of streptococci, staphylococci, and pneumococci. It is synergistic with aminoglycosides in the treatment of severe infections in neonates and young infants.

The impact of development on PK: Protein binding of ampicillin is 12-25 % in neonates. 10% of the drug is eliminated via glomerular filtration, 90% by tubular secretion Documented $T_{½}$ is about 30-90 min in adults, and about one hour in newborn infants [167-169].

The impact of hypothermia on PK: There are no studies assessing the effect of hypothermia on ampicillin PK.

Sedative Drugs

Midazolam (Table 8a, 8b)

Drug specificity: Midazolam is an imidazobenzodiazepine currently used for treatment of status epilepticus and to provide sedation in neonates and young infants.

The impact of development on PK: Midazolam is a lipophilic drug (logP 3.9) with a high protein binding capacity (97%). Midazolam is metabolized in the liver by CYP3A4 and CYP3A5 to a hydroxylated metabolite (1-OH-midazolam) with subsequent metabolism to 1-OH-midazolam-glucuronide by UGTs. Both metabolites are pharmacologically active where 1-OH-midazolam is nearly equipotent to the parent drug. Both metabolites are eliminated via the kidneys. Midazolam plasma CL reflects hepatic CYP3A4/5 activity after intravenous administration over 3 months of life [138].

The impact of hypothermia on PK: During hypothermia decreased hepatic and renal blood flow and reduced metabolic capacity of cytochrome P450 may lead to decreased Vd and CL resulting in prolonged renal elimination of active midazolam metabolites. In animal studies of post cardiac arrest hypothermia midazolam Vd and Cl are decreased [170]. Mild hypothermia decreases midazolam steady-state CL in a rat model of cardiac arrest [170, 171]. Biphasic midazolam concentration changes were documented during moderate hypothermia and rewarming but increases in Vd did not correspond to the expected Cpl [172]. During the hypothermic phase of CPB, midazolam plasma levels increase in pediatric patients [173]. Hypothermia influences midazolam pharmacokinetic parameters but the clinical applications of these changes are not yet understood. There are no PK data in neonates available and only one study in young infants undergoing hypothermia was published [174]. Midazolam PK studies during hypothermia [170, 172-175] (Table **8a**), and the potential impact of drug specificity on midazolam disposition is documented (Table **8b**).

Analgesic and Anaesthetic Agents

Fentanyl (Sufentanil, Alfentanil, Remifentanil), (Table 9)

Drug specificity: Fentanyl is a synthetic opioid, 50 -100 fold more potent than morphine, used for pain prevention and management in preterm and term neonates and young infants.

Table 8a. ***Midazolam*** **PK studies previously reported during hypothermia [105].**

Authors/year	Investigated group	Vd	CL
Kern *et al.*/1991 [173]	children on CPB	not studied	not studied
Fukuoka *et al.*/2004 [172]	adults	↑	↓
Hostler *et al.*/2010 [174]	healthy volunteers-adults	*NS*	↓ (AUC ↑)*
Zhou *et al.*/2011 [175]	animals	↓	↓
Empey *et al.*/2012 [170]	animals	↓	↓

**NS* no significant difference

Table 8b. Drug-dependent PK changes: an impact of drug specificity on *midazolam* biodisposition and action in neonates and young infants (vs adults).

I. Changes in Vd are:	II. Changes in CL are:
• Temperature-dependent • Age-dependent (body composition) • Drug - dependent (physical and chemical drug properties = lipophilic drug) • Disease-dependent (*e.g.*cardiac arrest)	• Temperature-dependent • Age-dependent (metabolic capacity of CYP3A4/A5) ↓ • Age - dependent (renal excretion of active metabolites:1OH-midazolam, 1-OH-midazolam-glucuronide = hydrophilic metabolites) • Drug - dependent (physical and chemical drug properties=97% protein binding drug) • Disease-dependent (*e.g.*cardiac arrest)

The impact of development on PK: Fentanyl is a lipophilic drug (logP 4), high clearance drug with a high hepatic extraction ratio. Fentanyl as well as other opioids (alfentanil, sufentanil) are metabolized via hepatic cytochrome CYP3A4 by oxidative N-dealkylation into inactive metabolites, and to a small extent excreted unchanged via the kidney. Vd in neonates and children is larger than in adults resulting in initial lower fentanyl plasma concentrations. Fentanyl CL rapidly increases at birth to values of 70 to 80% of adults that may lead to increased plasma concentrations [176-178].

The impact of hypothermia on PK: Experimental and clinical studies have shown a significantly smaller Vd and total CL but essentially unchanged fentanyl plasma concentrations during hypothermia (18 – 25 °C) [176, 177, 179]. During deep hypothermia (18-25 °C) fentanyl CL seems to be greatly reduced dependent on the target temperature [179]. In another experimental hypothermia model (32°C), plasma fentanyl concentrations increased mostly due to reduced hepatic blood flow and a reduction of CYP3A enzyme activity [180]. In comparison, several studies showed an initial decrease of fentanyl plasma concentrations during CPB due to an increased Vd caused by hemodilution and drug sequestration to the CPB circuit components. Plasma concentrations remain stable during hypothermic CPB indicating a reduced CL [181-183].

There are very limited experimental and clinical PK data in neonates and young infants, especially during hypothermia, available in the literature (Table **9**).

Morphine

Drug specificity: Morphine is the most commonly used opioid in neonatal and pediatric intensive care worldwide as a postoperative analgesic and as a sedative during mechanical ventilation [184].

The impact of development on PK. Morphine is a high hepatic CL, low protein binding drug that is metabolized by the liver to active metabolites morphine-6-glucuronide (M6G) and morphine-3-glucuronide (M3G) . Importantly the morphine metabolites have anti-analgesic c.q. strong analgesic effects which contribute to the overall change in PD parameters. Morphine CL increased with postmenstrual age till 6 - 12 months postnatally [185, 186]. Morphine plasma concentrations show large individual variability. Protein binding of morphine is reported to be around 20% in preterms vs 35% in adults published [187, 188]. In neonates with adverse effects of morphine, the plasma CL was decreased twofold [189-191].

The impact of hypothermia on PK: Hypothermia induced a decrease in morphine CL via a reduced elimination caused by a reduced liver and renal plasma flow (high hepatic CL, low protein binding drug), and decreased metabolic capacity. Cardiovascular effects (*e.g*, effects on blood pressure) of morphine during hypothermia seem to be related to increased morphine plasma concentrations in neonates undergoing total body cooling. In experimental settings morphine results in a significant increase in plasma concentrations of pituitary hormones and histamine (HIS) in hypothermic but not in normothermic animals [192, 193] Morphine plasma and cerebrospinal concentrations were significantly higher at 30°C. These results suggest that opioids could have detrimental effects in patients with poor cardiovascular reserve in which high doses of opiates and hypothermia may be used concomitantly. Bansinath *et al*. found a decreased Vd and total body CL in a dog model of moderate hypothermia (30°C) [194]. Apart from these changes in PK there is evidence that morphine affinity for the μ opioid receptor is reduced by hypothermia.[195, 196] In a neonatal trial assessing WBC in post asphyxiated neonates significantly higher morphine plasma levels were found in the hypothermic treatment group vs. normothermic nonasphyxiated neonates. Morphine concentrations are positively correlated to both morphine infusion rate, and cumulative morphine dose [56].

Propofol

Drug specificity: Propofol is a short acting anesthetic agent, recommended for intubation in neonatal and pediatric patients.

Table 9. ***Fentanyl*** **PK studies previously reported during hypothermia [51, 105, 182, 183].**

Authors/year	Investigated group	Vd	CL
Koren *et al.*/1987 [179]	animals	↓	↓
Koren *et al.*/1987 [179]	children	↓	↓
Petros at al./1995 [178]	adults on CPB	↑	*NS**
Statler *et al.*/2003 [16]	animals	not reported	↓
Pettifer *et al.* /2004 [180]	animals	not reported	*NS**
Fritz *et al.* /2005 [176]	animals	not reported	↓
Empey *et al.*/ 2012 [170]	animals	↓	↑

**NS* not significant

The impact of development on PK: Propofol is a highly protein bound (95-99%) and highly lipophilic drug (logP 3.8). It is mainly metabolized in the liver by glucuronidation at the C_1-hydroxyl end. Hydroxylation of the benzene ring to 4-hydroxypropofol may also occur via CYP2B6 and 2C9. Post-menstrual age and post-natal age contribute to the inter-individual variability of propofol CL with very fast maturation of CL in neonatal life during either intermittent bolus or continuous administration of propofol [197, 198].

The impact of hypothermia on PK: There are indications that propofol PK, and (PD) are affected by hypothermia. When using Bispectral Index (BIS) to titrate propofol dosing during CPB mild hypothermia reduced propofol requirements almost two-fold in adults [199, 200]. Importantly BIS monitoring is not validated under the age of 0.5-1 year and should be used with caution. When used as a continuous infusion during hypothermia increased plasma levels may occur [201]. There are no propofol PK data in neonates and young infants under conditions of hypothermia

Anticonvulsive and Neuroprotective Agents

Phenobarbital, (Table 10a, 10b)

Drug specificity: Phenobarbital, the 5 ethyl-5-phenyl substituted barbiturate is used as an anticonvulsive and neuroprotective drug in neonates and young infants.

The impact of development on PK: Phenobarbital is a lipophilic, long acting barbiturate. The Vd, CL and primarily low protein binding are age dependent: Vd decreases, whereas CL and protein binding increases with postnatal age. Developmental changes lead to reduced metabolism and renal excretion, resulting in the lowest CL in neonates. Phenobarbital is a drug with low hepatic CL that is mainly eliminated via the liver by CYP 2C19 enzyme and NADPH-cytochrome c. reductase. It is partly bound to protein (20-45%) with a logP of 1.47. The metabolites are excreted in the urine, and less commonly, in the feces.

The impact of hypothermia on PK: In hypothermic children (30-31°C) CL and Vd of pentobarbital and phenobarbital is suggested to be reduced as first described in critically ill children during HT [202, 203], as well as in one experimental study [204]. Data of PD of the different anticonvulsive drugs used in neonates or children available in the literature [205-207]. Filippi *et al* described increased plasma levels of phenobarbital with decreased CL in neonates treated for perinatal asphyxia with therapeutic hypothermia [58]. Two population PK/PD studies have been published recently showing no clinically relevant impact of HT on PK of phenobarbital [208, 209]. The most important mechanisms of reduced CL are: a. reduction of enzymatic processes, redistribution of blood flow (low hepatic CL drug) or decreased protein binding (low binding protein drug) that will influence PK. TDM is advised in these patients to monitor plasma levels during cooling and rewarming to prevent toxicity and withdrawal. The target range of the therapeutic phenobarbital serum concentrations is recommended: 10 (20) - 40 $\mu g \cdot mL^{-1}$ (Table **10a**, **10b**).

Topiramate

Drug specificity: Topiramate (TPM), 2, 3:4, 5-bis-*O*-(1-methyethylidene)-(beta)-D-fructopyranose sulfamate is used as an anticonvulsive drug. *The impact of development on PK:* 50 - 80% of topiramate is excreted unchanged [210].

The impact of hypothermia on PK: Topiramate CL and absorption are slower under hypothermia [57]. TDM of topiramate is not routinely recommended.

Neuromuscular Blocking Agents

Cisatracurium, Pancuronium, Rocuronium Vecuronium, Tubocurarine

Drug specificity: Neuromuscular blocking agents are used during hypothermia to prevent shivering in critically ill patients, in neonates and young infants as muscle relaxants during anesthesia and for facilitating endotracheal intubation.

The impact of development on PK: Reported age-dependent neuromuscular blocker requirements can be explained by changes in sensitivity, Vd, and muscle mass [211, 212].

The impact of hypothermia on PK: Miller *et al*. found decreased pancuronium CL 61% (at 29°) [213] whereas Ham *et al*. documented decreased tubocurarine CL from 44% (at 34°) to 61% (at 29°) [214]. Vecuronium Cl remaines unaltered during hypothermia in rats [215] but appears to be decreased in human adults [216]. Lower plasma levels with decreased CL during mild and deep hypothermia are found in children on CPB. Overall vecuronium requirements were greatly reduced during hypothermia due to altered PD [55]. Cisatracurium PK does not seem to be greatly altered in infants on mild hypothermic CPB although infusion rate decreases during hypothermia [217]. Overall there is evidence that PK, but especially PD is altered during hypothermia. Prolonged offset time of neuromuscular blocking agents and reduced CL are major temperature-dependent PK/PD changes, both based on experimental data [213-215, 218] and clinical studies in critically ill children [55, 217] and adults undergoing hypothermia [216], (Table **11**).

Inhaled Anesthetics

Hypothermia increases the solubility of volatile anesthetic agents in plasma, blood and tissue [219-221]. Induction and recovery of inhalational anesthesia are slower at lower temperatures due to a slower rate of increase and decrease of the alveolar anesthetic concentration caused by this increase in solubility [220, 221]. Hy-

Table 10a. *Phenobarbital* PK studies previously reported during hypothermia [51, 58, 105].

Authors/year	Investigated group	Vd	CL
Kalser *et al.*/1968 [204]	animals	not reported	↓
Kadar *et al.*/1982 [203]	children	↑	↓
Shaible *et al.*/1982 [202]	children	↓	↓
Filippi *et al.*/ 2011 [58]	neonates	↑	↓
Thoresen *et al.*/ 2003 [case report]	neonates	↑	↓

Table 10b. Drug-dependent PK changes: an impact of drug specificity on *phenobarbital* biodisposition and action in neonates and young infants (vs adults).

I. Changes in Vd are:	II. Changes in CL are:
• Temperature-dependent • Age-dependent (body composition) • Drug - dependent (physical and chemical drug properties =lipophilic drug, large Vd drugs, 45% protein binding drug) • Diseases-dependent (*e.g.* asphyxia)	• Temperature-dependent • Age-dependent (metabolic capacity of CYP 2C19, NADPH-cytochrome c. reductase) • Drug-dependent (physical and chemical drug properties, 45% protein protein binding drug) • Disease-dependent (low hepatic CL and low renal CL drug) • Drug-drug interactions

pothermia decreases the MAC (Minimum Alveolar Concentration): the end tidal concentration of a volatile anesthetic where 50 % of patients do not react with movement to surgical skin incision; the alveolar concentration directly represents the partial pressure of anesthetic in the central nervous system after a short equilibration period due to increasing solubility of the agent in the brain at decreasing temperatures and the effect of hypothermia in itself on anesthetic requirement [222].

The Impact of Hypothermia on Pharmacokinetics: Therapeutic Drug Monitoring Guiding Individual Dosage Adjustment

Key Points

***The impact of hypothermia on PK*:** a. for most drugs hypothermia might reduce drug absorption (*i.e.* the absorption rate), b. hypothermia results in different changing drug distribution (*i.e.* the volume of distribution = Vd increases, decreases, is unaltered or variable) especially decreased Vd of the peripheral compartment has been shown for *lipophilic drugs* (*e.g.*, anticonvulsants-diazepam, phenobarbital, analgesics - fentanyl, morphine or cardiovascular drugs - digoxin). For hydrophilic drugs the changes in Vd of the central compartment seems to be associated with underlying diseases c. hypothermia might reduce drug elimination (*i.e.* the total drug clearance = CL decreases overall or is rarely unaltered), especially shown for *high clearance drugs* excreted unchanged via the kidney (*e.g.*, antimicrobials - aminoglycosides, analgesics - midazolam), *high hepatic CL drugs* metabolized via liver (*e.g.* analgesics – morphine, fentanyl, sufentanil) or *high protein binding* drugs resulting to higher unbound fraction of drug in blood (*e.g.*, valproic acid).

The role of PK-PD under hypothermia *(Fig. 3)*: I. changes in plasma concentrations (Cpl_s) are related to potential PK changes under hypothermia: lower Cpl_s are related to reduced absorption and/or increased Vd whereas decreased Vd and/or decreased CL predispose to higher Cpl_s II. Different changes in Vd under hypothermia contribute to the individual loading dose of specific drugs (*e.g. phenobarbital, aminoglycosides*) III. Changes in CL under hypothermia result potentially in the reduction of the maintenance dosage regimen of high CL drugs, and specific drugs with a low therapeutic index, respectively *(e.g. morphine, midazolam, aminoglycosides*) d. Temperature - dependent changes seems to contribute to age-dependent and disease-dependent changes. IV. The potential impact of rewarming on PK is not yet well understood in neonates and young infants.

CONCLUSION

Hypothermia is used nowadays under a variety of conditions aimed at improving pharmacodynamic parameters in short and long term follow-up of individual patients or patient groups. With a few exceptions the altered PK of individual or combined drugs is not taken into account in the evaluation of the clinical outcome although both under and overdosing may have a profound effect on overall outcome. For individual drugs such as morphine, vecuronium and gentamicin data are available but a systematic approach to integrate the PK and PD of drugs is lacking. Recently the so-called Pharmacool trial, which startedin 2011,evaluates in a systematical way the potential effect of hypothermia on pharmacokinetics and pharmacodynamics of frequently used drugs in neonates treated for perinatal asphyxia In more detail the PK parameters during hypothermia and eventually during rewarming are determined [223]. A classical approach evaluating individual drug dosing and speed of elimination using kinetically guided therapy is nowadays increasingly replaced by a systematic approach being population PK-PD modeling [224-228].This approach uses nonlinear mixed effect modeling (NONMEM) that allows analysis of unbalanced and sparse datasets. Individual PK/PD is helpful to validate population PK/PD data in neonates treated for perinatal asphyxia, HIE and for comorbidities and to optimize potential neuroprotective effect of HT, efficacy and safety of frequently used drugs [229-232], and [28, 233-236]. Some authors even call this approach of evaluating the effect of temperature: thermopharmacology [209].

Apart from classical maturational covariates such as body weight and postmenstrual age the variability in drug response can be linked to a broad spectrum of variables including pathophysiological parameters and device dependent variables such as priming volume of ECLS systems. The possibility of combining datasets of

Table 11. ***Neuromuscular agents*** **PK studies previously reported during hypothermia [51, 105].**

Authors/year	Investigated group	Neuromuscular blocking agent	CL (%) diference HT vs NT groups
Miller *et al.*/ 1978 [213]	animals	pancuronium	↓ by 2% to 61%
Ham *et al.*/1978 [214]	animals	tubocurarine	↓ by 34% to 61%
Beaufort *et al.*/2001 [215]	animals	tecuronium	↓ *NS*
Caldwell *et al.*/2000 [216]	adults	vecuronium	↓ 11.3% per °C
Withington *et al.*/ 2000 [55]	children on CPB	tecuronium	↓ by 70% of IR*[1)]
Withington *et al.*/ 2011[217]	children on CPB	cisatracurium	↓ by IR*[2)]

*[1)] PK calculated by decreased infusion rate of vecuronium by 92 to 84 % in the deep and moderate HT

*[2)] PK calculated by decreased infusion rate of cisatracurium by 60% during CPB with moderate HT

NS no significant difference IR infusion rate

the same drug in different populations offers the possibility for internal and external validation studies. These data can and should be used for alternative trial designs, in-vitro trial simulations and will result in dose adjustment. This approach has recently be proven to be effective in analgesic drug studies as well as in studies combining data sets of propofol. In this way RCTs are conducted as proof of principle concepts resulting in benefit to the individual patient [236]. Moreover apart from the more classical approaches of designing studies recent literature has highlighted the importance of opportunistic sampling as an alternative approach which is increasingly indicated and approved by IRBs. In this way the concept of sparse data can be combined with a fast gain of information in these particular and difficult to investigate groups of patients.

The role of PK/PD is to individualize and optimize dosage regimens in acute situations to prevent insufficient or toxic drug action, to objectively document adverse effects of acute administered drugs, and to identify real risks of chronic morbidities in the short and long term follow - up phase (pharmacovigilance).

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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