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Effects of Hypothermia on Pharmacokinetics and Pharmacodynamics

A Systematic Review of Preclinical and Clinical Studies

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Abstract

Examples of clinical applications of therapeutic hypothermia in modern clinical medicine include traumatic cardiac arrest, ischaemic stroke and, more recently, acute perinatal asphyxia in neonates. The exact mechanism of (neuro)protection by hypothermia is unknown. Since most enzymatic processes exhibit temperature dependency, it can be expected that therapeutic hypothermia may cause alterations in both pharmacokinetic and pharmacodynamic parameters, which could result in an increased risk of drug toxicity or therapy failure. Generalizable knowledge about the effect of therapeutic hypothermia on pharmacokinetics and pharmacodynamics could lead to more appropriate dosing and thereby prediction of clinical effects. This article reviews the evidence on the influence of therapeutic hypothermia on individual pharmacokinetic and pharmacodynamic parameters. A literature search was conducted within the PubMed, Embase and Cochrane databases from January 1965 to September 2008, comparing pharmacokinetic and/or pharmacodynamic parameters in hypothermia and normothermia regarding preclinical (animal) and clinical (human) studies. During hypothermia, pharmacokinetic parameters alter, resulting in drug and

metabolite accumulation in the plasma for the majority of drugs. Impaired clearance is the most striking effect. Based on impaired clearance, dosages should be decreased considerably, especially for drugs with a low therapeutic index. Hypothetically, high-clearance compounds are affected more than low-clearance compounds because of the additional effect of impaired hepatic blood flow. The volume of distribution also changes, which may lead to therapy failure when it increases and could lead to toxicity when it decreases. The pH-partitioning hypothesis could contribute to the changes in the volumes of distribution for weak bases and acids, depending on their acid dissociation constants and acid-base status. Pharmacodynamic parameters may also alter, depending on the hypothermic regimen, drug target location, pharmacological mechanism and metabolic pathway of inactivation. The pharmacological response changes when target sensitivity alters. Rewarming patients to normothermia can also result in toxicity or therapy failure. The integrated effect of hypothermia on pharmacokinetic and pharmacodynamic properties of individual drugs is unclear. Therefore, therapeutic drug monitoring is currently considered essential for drugs with a low therapeutic index, drugs with active metabolites, high-clearance compounds and drugs that are inactivated by enzymes at the site of effect. Because most of the studies (74%) included in this review contain preclinical data, clinical pharmacokinetic/pharmacodynamic studies are essential for the development of substantiated dose regimens to avoid toxicity and therapy failure in patients treated with hypothermia.

Documentation of therapeutic hypothermia in modern clinical medicine started more than 200 years ago in 1803 as a Russian method of resuscitation.^[1] Examples of current clinical applications are traumatic cardiac arrest,^[2] ischaemic stroke,^[3] coronary artery surgery^[4] and traumatic intracranial hypertension after severe head injury.^[5] Another accepted indication is acute perinatal asphyxia in neonates. The exact mechanism of (neuro)protection is unknown, but hypothermia is believed to decrease apoptosis in infants and to interrupt early necrosis.^[6-10] In asphyxiated neonates, for example, hypothermia leads to a reduced metabolic rate and a decreased release of nitric oxide and excitotoxins, thereby reducing the likelihood of the development of neonatal encephalopathy.^[11,12]

Since most enzymatic processes exhibit temperature dependency, it can be expected that therapeutic hypothermia may cause alterations in both pharmacokinetic and pharmacodynamic parameters, which could result in an increased risk of drug toxicity or therapy failure.^[13] It has been shown that the influence of hypothermia on isolated pharmacokinetic and pharmacodynamic parameters may vary between drugs. Generalizable knowledge about the effect of therapeutic hypothermia on pharmacokinetics and pharmacodynamics could lead to more appropriate dosing and thereby prediction of clinical effects. This is especially important in asphyxiated neonates because of renal impairment and hepatic injury, and because of the highly variable and relative rapidly changing pharmacokinetic/pharmacodynamic parameters during the first months of life.^[14-20] Therefore, we conducted this systematic review to summarize the evidence on the effect of therapeutic hypothermia on pharmacokinetic/pharmacodynamic parameters in humans (clinical studies) and animals (preclinical studies).

1. Methods

1.1 Data Sources

A literature search was conducted within the PubMed, Embase and Cochrane databases from January 1965 to September 2008. The search terms in the selected databases included 'hypothermia', 'pharmacokinetics' and 'pharmacodynamics', and the searches were limited to the English language. In the PubMed database, the search was conducted using the corresponding National Library of Medicine MeSH search terms.

1.2 Study Selection

Duplicates were deleted from the search. Studies were eligible for inclusion if they met the following criteria on the basis of their titles and abstracts: (i) studies providing data on both hypothermia and normothermia; (ii) investigation of non-volatile agents; (iii) investigation of drugs or exogenous compounds used as markers for physiologic/metabolic functions; and (iv) access to the abstract or full text.

The remaining studies were retrieved as full-text and screened. Studies were excluded if they met one or more of the following criteria: (i) the publication was a review publication, i.e. it provided no new original data; (ii) the research was performed in a cardiological bypass setting; (iii) there was no description of pharmacokinetic/pharmacodynamic parameters; (iv) the effect could not be attributed to hypothermia only; or (v) there was no systemic hypothermia for *in vivo* studies. Finally, the retrieved studies were searched manually for additional references, to which the same inclusion and exclusion criteria were applied.

1.3 Definitions

'Therapeutic hypothermia' was defined as a deliberately induced lowered total body temperature (core temperature of 35°C or less) in subjects, with the purpose of improving clinical outcomes such as neuronal damage. This definition excluded an accidentally lowered body temperature as a consequence of, for example, drug adverse effects, drowning or a (post)operative complication. A low total body temperature could, for example, also be attributed to an adverse effect of a drug other than the drug under investigation. *In vitro/in situ* studies in hypothermic conditions were also defined as 'therapeutic hypothermia' when the influence of induced hypothermia on pharmacokinetic/pharmacodynamic parameters was studied. Therapeutic hypothermia was divided into multiple categories: (i) mild hypothermia (rectal temperature 35–36.5°C); (ii) moderate hypothermia (rectal temperature 32–35°C); and (iii) severe hypothermia (rectal temperature <32°C). The names and classification of these regimens are ambiguous in the literature.

If 'normothermia' was mentioned but no temperature was provided by the authors, this temperature was interpreted as 37°C for humans. Normothermia values for species other than humans can vary.

'Pharmacokinetic parameters' were defined as parameters that describe variability in plasma concentration-time profiles of drugs. Pharmacokinetic parameters were categorized into three groups: (i) absorption; (ii) distribution; and (iii) total clearance (CL).

'Total clearance' was defined as the total body clearance of a drug, regardless of its (metabolic) pathways. It was the sum of all individual (organ) clearance values. Terms such as 'metabolic clearance', 'systemic clearance' and 'body clearance' are referred to in this review as 'total clearance'.

'Pharmacodynamic parameters' were defined as parameters that describe variability in plasma concentration-effect profiles of drugs at the level of the target. Variability in plasma concentration-effect profiles comprises the onset of the effect, the duration of the effect and the time to recovery.

Studies were defined as 'comparative parallel' when the hypothermic subjects were compared with normothermic control subjects or reference values in the literature, or were defined as 'comparative crossover' when the hypothermic subjects were compared with themselves in normothermic conditions. Studies were defined as 'descriptive' when no comparison was made.

1.4 Data Extraction

The following data were extracted from the studies included in the review: (i) publication characteristics (first author and

year of publication); (ii) study characteristics (the species and number of subjects, model, design, administered drug, therapeutic group, route of administration, hypothermic regimen and evaluated pharmacokinetic/pharmacodynamic parameters); and (iii) effects of hypothermia.

1.5 Data Synthesis

Data regarding study characteristics and effects of hypothermia on pharmacokinetic/pharmacodynamic parameters were classified, extracted, grouped per pharmacokinetic/pharmacodynamic parameter and analysed. The effect of hypothermia on each pharmacokinetic or pharmacodynamic parameter was expressed as a relative difference (expressed as a percentage) of hypothermia compared with normothermia. The unit of analysis, therefore, is the effect of hypothermia on a single pharmacokinetic/pharmacodynamic parameter of an individual drug per subject species and study model. In case this relative difference was not provided by the authors in the study publication, it was calculated from the provided data, using equation 1:

$$\text{Relative difference} = \frac{\text{value hypothermia} - \text{value normothermia}}{\text{value normothermia}} \times 100\% \quad (\text{Eq. 1})$$

The investigated pharmacokinetic parameters regarding absorption were the absorption rate constant (k_a) and the onset of absorption, and the parameter regarding distribution was the apparent volume of distribution (V_d). The pharmacokinetic parameters investigated with regard to CL were hepatic clearance (CL_H), renal clearance (CL_R), biliary clearance (CL_{bil}), cytochromal intrinsic clearance (CL_{int}), the Michaelis-Menten constant (K_m), the maximum rate of the enzymatic process (V_{max}), the elimination rate constant (k_e) and appearance of compounds (the parent compound or metabolites) in the plasma. The following pharmacodynamic parameters were investigated: the concentration of the drug producing $n\%$ of the maximum effect (EC_n), the maximal effect (E_{max}), the steepness of the concentration-effect curve (also known as the shape factor or the Hill factor [the γ -value]), the rate constant for drug equilibration between the plasma and the effect site (k_{e0}), the onset of the effect and the duration of the effect.

2. Results

The study selection is shown in figure 1. A total of 919 publications were identified after the computerized searches. From these 919 publications, 182 publications were eligible for

inclusion according to the criteria on the basis of their titles and abstracts. After retrieval of the full papers and screening, 151 publications were excluded. Eight publications were added manually after cross-referencing, which resulted in a dataset of 39 included publications.

The detailed study characteristics are summarized in table I. The 39 publications provided evidence on 69 different associations of the effects of hypothermia on pharmacokinetic and/or pharmacodynamic parameters. Several publications described research in more than one study model or described more than one drug, or the study was conducted in more than one hypothermic regimen, or more than one pharmacokinetic/pharmacodynamic parameter was described. Twenty-six percent of the dataset comprised studies in humans (clinical studies). Of these studies, one study was conducted in neonates and two studies in children. Of the 43 animal studies (preclinical studies), 32 studies were conducted in rodents. The majority of these (53 of 58) had a comparative design. Of these studies with a comparative design, 67% had a comparative parallel design. Pharmacokinetic/pharmacodynamic parameters at temperatures below 32°C (severe hypothermia) were most frequently studied (69%). Neuromuscular-acting agents (22%) and cardioactive agents (19%) were the most frequently investigated drugs.

Sixty-nine percent of all studies described only pharmacokinetic parameters, 24% described only pharmacodynamic parameters and the remaining 7% described both pharmacokinetic and pharmacodynamic parameters.

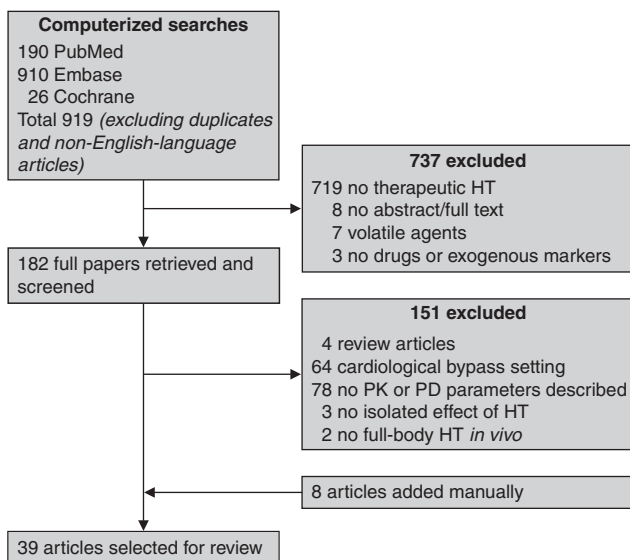


Fig. 1. Study flow diagram. HT=hypothermia; PD=pharmacodynamic; PK=pharmacokinetic.

Table I. Characteristics of studies included in the systematic review

Characteristic	No. (%)
Species^a [n=58]	
Human	15 (26)
Animal	43 (74)
rat	29 (50)
pig	5 (9)
rabbit	3 (5)
cat	2 (3)
mouse	2 (3)
dog	1 (2)
guinea-pig	1 (2)
Model^a [n=58]	
<i>In vivo</i>	33 (57)
<i>In vitro</i>	23 (40)
<i>In situ</i>	3 (5)
Design^a [n=58]	
Descriptive	1 (2)
Comparative	53 (91)
parallel	39 (67)
crossover	15 (26)
Not applicable/unknown	3 (5)
Route of administration in <i>in vivo</i> studies^a [n=33]	
Intravenous	31 (94)
Oral	1 (3)
Both intravenous and oral	1 (3)
Therapeutic group^{a,b,c} [n=58]	
Anaesthetics [local]	6 (10)
Analgesics	7 (12)
Antibacterials	3 (5)
Anticonvulsants	4 (7)
Cardioactive/cardiovascular agents	11 (19)
Cytotoxic agents	2 (3)
Neuromuscular-acting agents	13 (22)
Sedatives/anxiolytics	2 (3)
Other drugs and agents	10 (17)
Described parameters^a [n=58]	
Pharmacokinetic only	40 (69)
Pharmacodynamic only	14 (24)
Both pharmacokinetic and pharmacodynamic	4 (7)
Comparative hypothermic regimens^{a,b,d} [n=87]	
35–36.5°C [mild HT]	5 (6)
32–35°C [moderate HT]	22 (25)

Continued next page

Table I. Contd

Characteristic	No. (%)
<32°C [severe HT]	60 (69)
Year of publication [n=39]	
1960–1969	5 (13)
1970–1979	5 (13)
1980–1989	10 (26)
1990–1999	7 (18)
2000–2008	12 (31)
a A publication can describe multiple models.	
b A publication can describe multiple drugs/agents.	
c A drug can be placed in more than one therapeutic group.	
d A publication can compare multiple hypothermic regimens.	

HT = hypothermia.

2.1 Effect of Hypothermia on Pharmacokinetic Parameters

2.1.1 Absorption

Results regarding absorption are presented in table II.

Preclinical data (two units of analysis): The k_a values of pentobarbital (pentobarbitone), levodopa and uracil were decreased by 30–44% during moderate and severe hypothermia (table II).^[21,23] A slower rate of availability was observed for levodopa and uracil. The rate of availability of levodopa was more affected by hypothermia than that of uracil.

Clinical data (one unit of analysis): For phenazone (antipyrene), the onset of absorption was delayed by 30 minutes, but the rate of absorption was unaltered during severe hypothermia.^[22]

Interpretation

Absorption of drugs is affected by many factors; physiological factors (such as the gastric and duodenal pH), as well as the physicochemical properties of the drug (such as the acid dissociation constant [pKa] and lipid solubility), are involved.

Table II. Effect of hypothermia (HT) on the absorption rate constant (k_a)

Study	Species and model	Drug/agent	Thermic regimen	Relative difference in k_a in HT group vs NT group
Stavchansky and Tung ^[21]	Rat; <i>in situ</i> (n=12)	Pentobarbital (pentobarbitone)	Severe HT (38°C vs 20°C)	Decreased 44%
	Rat; <i>in situ</i> (n=NA)	Levodopa	Moderate and severe HT (33.8–35.0°C vs 22.0–28.3°C)	Decreased ~40%
	Rat; <i>in situ</i> (n=NA)	Uracil	Moderate and severe HT (33.8–35.0°C vs 22.0–28.3°C)	Decreased ~30%
Shepherd et al. ^[22]	Human; <i>in vivo</i> (n=1)	Phenazone (antipyrene)	Severe HT (36.8°C vs 28.0°C)	Unaltered

NA = data not available; **NT** = normothermia.

In vitro, active drug transport (via multidrug resistance protein-1) during moderate hypothermia changed for the investigated substrates, but passive diffusion was not affected. In preclinical studies, the k_a values were decreased. In one clinical study, the absorption rate of phenazone was unaltered, but the onset of absorption was delayed.^[22] Hypothermia can result in a slower rate of availability. The time of onset may be delayed and the magnitude of the pharmacological response of the drug may be decreased. These studies examined the rate of absorption rather than the extent.

The overall effect of hypothermia on drug absorption is a decreased rate. A prolonged time to reach the maximum concentration can be observed. Plasma concentrations after oral administration are more variable than after parenteral administration when absorption changes during hypothermia. In addition, all patients with diseases for which hypothermia is used clinically as a neuroprotective strategy/therapy have reduced gastrointestinal motility, which adds to the variability of blood drug concentrations. When using drugs that only have oral formulations, such as sildenafil for pulmonary hypertension, one should be very careful with administration during hypothermia.

A recently published study by Filippi et al.^[24] concluded that topiramate plasma concentrations after oral administration did not significantly differ between neonates treated with mild (33–34°C) and deep (30–33°C) hypothermia. According to the authors, plasma topiramate concentrations appeared higher during hypothermia than reported in normothermic infants and oral topiramate absorption was maintained during hypothermia. Whether the limited sample size could have attributed to the nonsignificance of their findings was not determined.

2.1.2 Distribution

Study results regarding the V_d are displayed in table III.

Preclinical data (six units of analysis): Five of the six units reported that the V_d decreased (by 11–40%, median 32%) during moderate and severe hypothermia.^[25–28] One unit reported a 27% increase in the V_d during severe hypothermia.^[29] One study observed a decreased volume of the central compartment.^[25]

Clinical data (seven units of analysis): Two of the seven units reported a 20% decrease in the V_d during moderate and severe hypothermia;^[22,30] three units reported an unaltered V_d during moderate hypothermia;^[31,32,35] and two units reported that the V_d increased (by about 25% and by 83%) during moderate and severe hypothermia.^[33,34]

Interpretation

The V_d of drugs is affected by both physiological factors (such as global blood perfusion and the blood pH) and the physicochemical properties of the drug (such as protein binding capacity, lipid solubility and tissue binding capacity). All of these factors and drug properties can alter during hypothermia, as described below.

Global Blood Perfusion

During hypothermia, there is a redistribution of blood away from the gastrointestinal tract, extremities, kidneys and liver towards the coronary and cerebral circulations.^[36] Vasodilatation of skeletal muscles contributes to this redistribution.^[37] The intravascular distribution volume is reported to be decreased by 10–35% in animal models.^[38–42] A decreased cardiac output and water sequestration are also factors contributing to an altered V_d .^[25,43]

Blood pH

The blood pH is affected by hypothermia. At lower temperatures, the carbon dioxide partial pressure (pCO_2) decreases and the pH increases. A 10°C temperature reduction will result in an *in vivo* pH increase from 7.40 to 7.55 when there is no (adjusted) blood-gas management or intravenous (acidic) fluid administration.^[44] Depending on their pKa and acid-base status, drugs are more or less ionized when a pH shift occurs. At a pH shift from 7.40 to 7.55, the ionization of the weak base lidocaine (lignocaine) [pKa 7.9] decreases significantly from

Table III. Effect of hypothermia (HT) on the apparent volume of distribution (V_d)

Study	Species and model	Drug/agent	Thermic regimen	Relative difference in V_d in HT group vs NT group
Koren et al. ^[25]	Pig; <i>in vivo</i> (n = 7)	Gentamicin	Severe HT (37°C vs 29°C)	Decreased 32%
	Pig; <i>in vivo</i> (n = 7)	Theophylline	Severe HT (37°C vs 29°C)	Decreased 11%
Miller et al. ^[26]	Cat; <i>in vivo</i> (n = 18)	Pancuronium	Moderate and severe HT (39°C vs 34°C vs 29°C)	Decreased 40% at 34°C and 35% at 29°C
Ham et al. ^[27]	Cat; <i>in vivo</i> (n = 16)	Tubocurarine	Moderate and severe HT (39°C vs 34°C vs 28°C)	Decreased 18% at 34°C and 22% at 28°C (NS)
Bansinath et al. ^[28]	Dog; <i>in vivo</i> (n = 18)	Morphine	Severe HT (37°C vs 30°C)	Decreased 33%
Tortorici et al. ^[29]	Rat; <i>in vivo</i> (n = 6)	Chlorzoxazone	Severe HT (37°C vs 30°C)	Increased 27%
Shepherd et al. ^[22]	Human; <i>in vivo</i> (n = 8)	Phenazone (antipyrene)	Moderate and severe HT (36.8°C vs 28.0–34.3°C)	Decreased 20% (NS)
Schaible et al. ^[30]	Human; <i>in vivo</i> (n = 11)	Pentobarbital (pentobarbitone)	Severe HT (37°C vs <32°C)	Decreased 20%
Iida et al. ^[31]	Human; <i>in vivo</i> (n = 14)	Phenytoin	Moderate HT (37°C vs 34°C)	Unaltered
Heier et al. ^[32]	Human; <i>in vivo</i> (n = 7)	Neostigmine	Moderate HT (37°C vs 34°C)	Unaltered
Fukuoka et al. ^[33]	Human; <i>in vivo</i> (n = 15)	Midazolam	Moderate HT (37°C vs 32–34°C)	Increased 83%
Kadar et al. ^[34]	Human; <i>in vivo</i> (n = 4)	Phenobarbital (phenobarbitone)	Severe HT (37°C vs 30–31°C)	Increased ~25%

NS = not significant; NT = normothermia.

76% to 69%.^[45] In this case, 7% more un-ionized drug can cross the blood-brain barrier, causing an enhanced cerebral effect. Likewise, the incidence of (severe) adverse reactions such as cardiac arrhythmias could also be increased.^[46] If the blood pH changes due to hypothermia, the V_d of drugs with pKa values between approximately 7 and 8 are most affected. Based on the pH-partitioning hypothesis, the V_d of weak bases will increase, whereas the V_d of weak acids will decrease. In clinical trials in hypothermic neonates, mechanical ventilation settings were adjusted in order to maintain an *in vivo* hypothermic pH of 7.4 and a pCO₂ of 5.3 kPa (40 mmHg) [pH-stat].^[44] In contrast, in the alpha-stat method, the blood pH is adjusted to a pH of 7.4 measured at 37°C. From a pharmacological point of view, considering toxicity and adverse effects, the pH-stat method seems to be preferable to the alpha-stat method.

Plasma Protein Binding Capacity

Plasma protein binding was determined in four units of analysis. *In vivo* studies (with phenytoin in humans and chlorzoxazone in rats) demonstrated unaltered plasma protein binding,^[29,31] while *in vitro* studies demonstrated (for sulfanilamide and lidocaine) altered plasma protein binding (increased by 65% at 17°C and decreased by 24% at 24°C).^[46,47]

Plasma protein binding is observed to be increased, decreased and unaltered. Therapeutic regimens in *in vitro* studies (17°C, 24°C and 25°C; severe hypothermia) are lower than in *in vivo* studies (30°C and 34°C). If there is an effect of hypothermia on protein binding, the effect will probably be larger at lower temperatures. This could explain why altered protein binding has been observed particularly in *in vitro* studies. For sulfanilamide, such an increase was observed. In contrast, for lidocaine, decreased plasma protein binding was observed at 24°C. One should be aware that *in vivo* determination of plasma protein binding during hypothermia is not accurate when analysis is carried out at room temperature (or 25°C). After collection of the blood sample, hypothermic blood warms up towards room temperature and drug-protein binding forms a new equilibrium before the analysis is carried out. This hampers adequate interpretation of these results.^[31] It therefore remains unclear what the effect of mild and/or moderate hypothermia will be on plasma protein binding.

Lipid Solubility

Lipid solubility (or lipophilicity) is affected by temperature. A study by Perlovich et al.^[48] demonstrated that lower temperatures decrease transfer processes in water/n-octanol systems of the β -adrenoceptor antagonists atenolol and pindolol. Decreased transfer into lipid tissue could contribute to a decrease in the V_d *in vivo*.

Tissue Binding Capacity

The tissue binding capacity of drugs could be affected by hypothermia. The tissue binding capacity of phenytoin in rats has been observed to be increased by heat treatment.^[49] Hypothermia may also induce changes in protein dimensional conformation, leading to an altered tissue binding capacity.

All factors mentioned above can alter in hypothermic conditions, causing an overall altered V_d . Depending on the hypothermic regimen and the physicochemical properties of the drug, each of these factors will be influenced differently. An altered V_d has consequences for the (loading) dose, which should be adjusted in the clinical setting. An increased peripheral V_d in hypothermia may cause subtherapeutic plasma concentrations, which could result in therapy failure. A decreased V_d could result in drug toxicity. The ionization status of drugs contributes to the V_d but plays a minor role in mild/moderate hypothermia or when the blood pH is corrected. The effect of hypothermia on the V_d has to be determined for every drug individually.

2.1.3 Total Clearance

The results regarding the effect of hypothermia on CL are displayed in table IV.

Preclinical data (27 units of analysis): All units showed a decrease in CL (by 2–84%, median 50%) during moderate and severe hypothermia, except for one, which showed no change in CL_R during moderate hypothermia.^[61]

Clearance of the high-clearance compound indocyanine green was affected more than clearance of the low-clearance compound *S*-acenocoumarol (84% vs 34%), and clearance of indocyanine green was affected more than clearance of phenolsulfonphthalein (81% vs 61% at 28°C), a low-clearance compound.

Studies investigating the K_m and V_{max} reported an increase in the K_m of at least 60% at 26°C and an unaltered V_{max} .^[29,50,51] *In vitro* studies investigating specific cytochrome P450 (CYP) isoenzymes (CYP3A4 and 2E1) observed a decrease in clearance for both isoenzymes of at least 31% at 32°C.^[29,52] The total metabolite formation and metabolite appearance in plasma were decreased.^[31,64] For pancuronium, the amount of the 3-OH metabolite was decreased; however, the amount of the 17-OH metabolite in plasma was increased.^[26]

CL_{bil} was reported to be decreased during hypothermia for most studied drugs (7 of 8). CL_{bil} of just vecuronium itself was reported to be unaltered, whereas CL_{bil} of the vecuronium metabolite was decreased.^[59] CL_{bil} of pancuronium was unaltered at 34°C but decreased by 40% at 29°C.^[26] Biliary flow was decreased, and the appearance of the drug in the bile was delayed.^[26,54,55,58,64]

Table IV. Effect of hypothermia (HT) on total clearance (CL)

Study	Species and model	Drug/agent	Thermic regimen	Relative difference in CL in HT group vs NT group
Tortorici et al. ^[29]	Rat; <i>in vitro</i> (n=8)	Chlorzoxazone	Severe HT (37°C vs 30°C)	K _m increased 116% V _{max} unaltered CL _{int} of CYP2E1 decreased 44%
	Rat; <i>in vivo</i> (n=6)	Chlorzoxazone	Severe HT (37°C vs 30°C)	CL decreased 54% k _e decreased 66% Urinary metabolite excretion decreased 76%
McAllister et al. ^[50,51]	Rat; <i>in vitro</i> (n=12)	Verapamil	Severe HT (37°C vs 26°C)	K _m increased 152% and 109% V _{max} unaltered
	Rat; <i>in vitro</i> (n=12)	Propranolol	Severe HT (37°C vs 26°C)	K _m increased 61% and 60% V _{max} unaltered
	Rat; <i>in vitro</i> (n=12)	Quinidine	Severe HT (37°C vs 26°C)	Metabolism decreased >50%
Fritz et al. ^[52]	Pig; <i>in vitro</i> (n=6)	Fentanyl	Severe HT (37.7°C vs 31.6°C)	Conversion rate of CYP3A4 decreased 31% at 32°C and 52% at 26°C
Kalser et al. ^[47]	Rat; <i>in vitro</i> (n=NA)	Sulfanilamide	Severe HT (37°C vs 25°C vs 17°C)	CL _H decreased (ND) CL _{bil} decreased 69% at 25°C and 88% at 17°C
Kalser et al. ^[53]	Rat; <i>in vitro</i> (n=NA)	Procaine	Severe HT (37°C vs 25°C vs 17°C)	CL _H decreased (ND) CL _{bil} decreased 64% at 25°C and 91% at 17°C
		Pentobarbital (pentobarbitone)	Severe HT (37°C vs 30°C vs 25°C vs 20°C)	CL _H decreased ~50% at 30°C, ~67% at 25°C and 75% at 20°C ^a Appearance of metabolites in blood decreased 32% at 30°C, 50% at 25°C and 79% at 20°C CL _{bil} decreased 71% at 30°C, 91% at 25°C and 94% at 20°C Appearance in bile delayed 4 min at 30°C and 29 min at 20°C Bile flow decreased 66% at 25°C Hepatic bile production decreased 49% at 30°C and 78% at 25°C Less metabolites excreted in bile
Kalser et al. ^[54,55]	Rat; <i>in vitro</i> (n=NA)	Atropine	Severe HT (37°C vs 25°C and 17°C)	CL _{bil} decreased 38% at 17°C and 77% at 25°C C _{max} in bile delayed 4-fold at 17°C vs 37°C Rate of bile flow decreased 67% at 17°C and 88% at 25°C Only appearance of metabolized atropine in bile No appearance of unchanged atropine in bile
Mortensen and Dale ^[56]	Rat; <i>in vitro</i> (n=NA)	Alcohol (ethanol)	Severe HT (37°C vs 27°C, 17°C and 7°C)	CL _H decreased 38% at 27°C, 83% at 17°C and 75% at 7°C
		Diazepam	Severe HT (37°C vs 27°C, 17°C and 7°C)	CL _H decreased 29% at 27°C, 47% at 17°C and 72% at 7°C
		Oxazepam	Severe HT (37°C vs 27°C, 17°C and 7°C)	CL _H decreased 42% at 27°C, 48% at 17°C and 48% at 7°C

Continued next page

Table IV. Contd

Study	Species and model	Drug/agent	Thermic regimen	Relative difference in CL in HT group vs NT group
Daemen et al. ^[57]	Rat; <i>in vivo</i> (n=8)	S-acenocoumarol	Moderate HT (37.5°C vs 32.5°C)	CL _H decreased 34%
		Indocyanine green	Moderate HT (37.5°C vs 32.5°C)	CL _H decreased 84%
Nishida et al. ^[58]	Rat; <i>in vivo</i> (n=NA)	Indocyanine green	Moderate and severe HT (37°C vs 32°C and 28°C)	CL decreased 53% at 32°C and 81% at 28°C CL _{bil} decreased 54% at 32°C and 90% at 28°C Appearance in bile delayed
		4-FD	Moderate and severe HT (37°C vs 32°C and 28°C)	CL _R decreased 41% at 28°C CL decreased 43% at 28°C (CL and CL _R increased at 32°C [NS])
		Phenolsulfonphthalein	Moderate and severe HT (37°C vs 32°C vs 28°C)	CL decreased 48% at 32°C and 62% at 28°C k _e decreased 38% at 32°C and 52% at 28°C CL _{bil} ^b decreased 31% at 32°C and 62% (NS) at 28°C
Beaufort et al. ^[59]	Rat; <i>in vitro</i> (n=22)	Vecuronium	Severe HT (38°C vs 28°C)	CL _{bil} of vecuronium unaltered CL _{bil} of metabolite decreased 11% (NP)
Lundgren-Eriksson et al. ^[60]	Mouse; <i>in vivo</i> (n=24)	Doxorubicin	Severe HT (37°C vs 28°C)	CL ^b decreased 29%
		Epirubicin	Severe HT (37°C vs 28°C)	CL ^b decreased 19%
Koren et al. ^[25]	Pig; <i>in vivo</i> (n=7)	Gentamicin	Severe HT (37°C vs 29°C)	CL decreased 51% k _e decreased 27%
Satas et al. ^[61]	Pig; <i>in vivo</i> (n=16)	Gentamicin	Moderate HT (39°C vs 35°C)	CL _R unaltered
Ham et al. ^[27]	Cat; <i>in vivo</i> (n=16)	Tubocurarine	Moderate and severe HT (39°C vs 34°C and 28°C)	CL decreased 44% at 34°C and 61% at 28°C
Miller et al. ^[26]	Cat; <i>in vivo</i> (n=18)	Pancuronium	Moderate and severe HT (39°C vs 34°C and 29°C)	CL decreased 2% at 34°C and 61% at 29°C Appearance of less 3-OH metabolite in plasma Appearance of more 17-OH metabolite in plasma CL _{bil} decreased 40% at 29°C CL _{bil} unchanged at 34°C Appearance in bile delayed 6 min at 34°C and 24 min at 29°C
Bansinath et al. ^[28]	Dog; <i>in vivo</i> (n=18)	Morphine	Severe HT (37°C vs 30°C)	CL decreased 70%
Iida et al. ^[31]	Human; <i>in vivo</i> (n=14)	Phenytoin	Moderate HT (37°C vs 34°C)	CL decreased 67% k _e decreased 50% Metabolite plasma concentration decreased (NP)
Heier et al. ^[32]	Human; <i>in vivo</i> (n=7)	Neostigmine	Moderate HT (37°C vs 34°C)	CL unaltered
Roka et al. ^[13]	Human; <i>in vivo</i> (n=16)	Morphine	Moderate HT (37°C vs 33–34°C)	CL ^a decreased 22%

Continued next page

Table IV. Contd

Study	Species and model	Drug/agent	Thermic regimen	Relative difference in CL in HT group vs NT group
Leslie et al. ^[62]	Human; <i>in vivo</i> (n=6)	Propofol	Moderate HT (37°C vs 34°C)	CL decreased 25% (NS)
Caldwell et al. ^[63]	Human; <i>in vivo</i> (n=12)	Vecuronium	Mild and moderate HT (>37°C vs 36–36.9°C, 35–35.9°C and <35°C)	CL decreased 11.3% per °C
Shepherd et al. ^[22]	Human; <i>in vivo</i> (n=8)	Phenazone (antipyrine)	Moderate and severe HT (36.8°C vs 28.0–34.3°C)	CL decreased 45%

a Estimated by the authors.

b Provided by the authors as the area under the plasma concentration-time curve.

4-FD=fluorescein isothiocyanate-dextran; **CL_{bil}**=biliary clearance; **CL_H**=hepatic clearance; **CL_{int}**=intrinsic clearance; **CL_R**=renal clearance; **C_{max}**=maximum plasma concentration; **CYP**=cytochrome P450; **k_e**=elimination rate constant; **K_m**=Michaelis-Menten constant; **NA**=data not available; **ND**=not determinable; **NP**=data not provided by authors; **NS**=not significant; **NT**=normothermia; **V_{max}**=maximum rate of the enzymatic process.

Different studies reported that CL_R of gentamicin was unaltered^[25] or decreased by 51%^[58] and that CL_R of fluorescein isothiocyanate-dextran (4-FD) was decreased by 41%.^[61]

Renal blood flow was observed to be decreased during hypothermia. According to Greven,^[65] the glomerular filtration rate (GFR) in rats decreased at temperatures lower than 30°C and normalized when a temperature of 30°C was reached. Nishida et al.^[58] observed that the GFR did not decrease when the temperature was at least 32°C but did decrease at temperatures below 32°C.

Clinical data (four units of analysis): All units showed a decrease in CL (22–25%) during mild and moderate hypothermia, except for one that did not show a change in CL during moderate hypothermia.^[32]

Interpretation

All studies observed a decrease in CL, except for two that showed no change.^[32,61] The influence of hypothermia on CL is discussed in terms of the influence on CL_H, CL_R and CL_{bil}.

Hepatic Clearance

CYP enzymes are responsible for the majority of drug metabolism in the liver. These reactions are oxidative reactions. As demonstrated by Tortorici et al.^[29] and by McAllister et al.,^[50,51] the affinity of the enzyme for the substance is decreased (with an increased K_m), while the V_{max} remains unaltered during hypothermia.

The rate of enzymatic conversion is temperature dependent according to enzyme kinetics. Enzymes are proteins, and an alteration in temperature results in altered enzyme activity due to lower kinetic energy, which reduces drug-enzyme collisions. This results in slower metabolic activity of enzymatic processes and thus less (in)activation of drugs and metabolite formation. The metabolic activity of oxidative enzymatic reac-

tions also depends on factors such as the affinity of oxygen for the ferric molecule in the enzyme, its haem group and the rate of the redox reactions. These factors are temperature-dependent reactions and could be slowed down during hypothermia.^[66]

The dimensional shape of proteins changes with thermal conditions. Fewer drug molecules fit on the active site of the enzyme if its dimensional shape is changed. The consequence of hypothermia is that there is less intrinsic activity between the drug molecule and the conversion enzyme, resulting in a decreased drug conversion rate.

The intracellular location of the metabolic process also contributes to the effect of hypothermia on CL_H. Elimination processes in the soluble part of the cell (the cytoplasm) seem to be more thermosensitive than processes on the cytoplasmic site of the endoplasmic reticulum, which affects enzyme reactions such as demethylation and hydroxylation. Processes in the cytoplasm seem to be more thermosensitive than processes in the lumen of the endoplasmic reticulum, such as the uridine diphosphate glucuronyltransferase reaction.^[56] Alterations in temperature also change membrane fluidity, which affects the conformation of membrane-bound enzymes.^[67]

The influence of hypothermia on CL_H of high-clearance and low-clearance drugs has been investigated. Indocyanine green is a substance with a high hepatic extraction ratio (90%) and is used to estimate hepatic blood flow.^[68] Phenolsulfonphthalein and S-acenocoumarol are examples of drugs with low hepatic extraction ratios. Clearance of indocyanine green was affected more by hypothermia than clearance of low-clearance drugs, probably because of impaired hepatic blood flow. Decreased cardiac output and blood redistribution from the liver impair hepatic blood flow.

Decreased metabolic conversion of drugs results in higher serum concentrations of the administered compound, which

may cause more toxicity and adverse effects. For morphine, an increased incidence of hypotension was observed.^[28] If the unchanged drug is inactivated by metabolism, the action of the drug will last longer. In contrast, if the administered drug is a prodrug, it will take longer for any effect to occur. Toxicity could also decrease with decreased metabolic conversion when the metabolites of the parent compounds have toxic features. Moreover, the metabolites may also accumulate in the plasma because of impaired clearance and excretion.

The clinical effect of administered drugs with (multiple) active metabolites, such as lidocaine and midazolam, will be unpredictable during hypothermia. Drugs that are not inactivated or drugs that are inactivated by just one single hepatic metabolism step (such as clonazepam) are preferable because of their more predictable clinical effect.

The extent of bioavailability has not been investigated, and the effect of this can only be assumed. Bioavailability depends on the absorption (see section 2.1.1) and on the first-pass effect (i.e. the activity of the involved hepatic enzymes and the CL_H ratio). Changed clearance and absorption could result in increased or decreased bioavailability. The contribution of clearance to the extent of bioavailability will be bigger for drugs with a large first-pass effect. This also favours parenteral administration over oral administration.

Renal Clearance

Elimination of drugs by the kidneys is a main route for excretion of hydrophilic drugs and hydrophilic conjugative metabolites. CL_R of the substance 4-FD was decreased by 41% at 28°C. 4-FD is excreted mainly by glomerular filtration.^[58] Aminoglycosides are almost completely excreted unchanged by the kidneys through filtration. Therefore, gentamicin clearance depends mainly on the GFR. Filtration is a passive transport and requires no energy. Koren et al.^[25] observed decreased gentamicin clearance due to a decreased GFR. Satas et al.^[61] found no difference in gentamicin clearance between the normothermia and hypothermia groups in newborn pigs. No change in the GFR was observed, but a decreased creatinine concentration was observed, which could be explained if mild hypothermia decreases creatinine synthesis. If creatinine synthesis is decreased by hypothermia, interpretation of renal function based on creatinine would be misleading.^[61]

The effect of hypothermia on tubular secretion is still unknown. Hypothermia could reduce tubular secretion or reabsorption because renal tubular transporters possibly exhibit temperature-dependent activity.^[37] Under a temperature of 30–32°C, the GFR was observed to be decreased. This could be due to an auto-regulation function for maintenance of

homeostasis to keep glomerular filtration function constant.^[58] Decreased cardiac output, increased blood viscosity, cold-induced vasoconstriction, blood redistribution and increased renal renin secretion are assumed to be contributing factors.^[69-71] A recently published study studied the pharmacokinetics of gentamicin. Liu et al.^[72] observed that hypothermia of 33.5°C did not affect serum gentamicin clearance in 55 encephalopathic infants. This result corresponds with the results demonstrated by Satas et al.^[61] in newborn pigs.

Biliary Clearance

Decreased CL_{bil} could be caused by decreased bile flow (due to impaired hepatic blood flow) and/or decreased activity of active hepatobiliary transport. *In vitro* experiments have demonstrated decreased bile flow during hypothermia.^[54,55,64] Transport by hepatobiliary transport mechanisms is impaired. For organic cations, cardiac glycosides and bile salts, carrier-mediated transport systems have been identified in the rat liver. Transport of these cations occurs against the electrochemical membrane gradient. Decreased CL_{bil} of the vecuronium metabolite, an organic cation, and indocyanine green, which is excreted predominantly in the bile via an active multi-specific organic anion transport system, could also be (partially) caused by decreased activity of these transporters.^[58,73-75]

Altered clearance has consequences for the maintenance dose rate. In the case of impaired clearance, the maintenance dose rate should be adjusted by lowering the dose or by prolonging the dosing interval to prevent toxicity. One should be aware that in hypothermia, maintenance doses should be decreased considerably, especially for drugs with a low therapeutic index. Hypothetically, dosages of high-clearance drugs should be adjusted more than those of low-/intermediate-clearance drugs during hypothermia. The data in our review are too limited to confirm this hypothesis. For example, in hypothermic neonates, lower doses of lidocaine have to be administered for convulsion control, but therapeutic drug monitoring is considered essential.^[76]

2.2 Effect of Hypothermia on Pharmacodynamic Parameters

The results regarding pharmacodynamic parameters are displayed in table V.

Preclinical data (12 units of analysis): For targets (such as acetylcholine receptors and cholinesterase) of neuromuscular agents (pancuronium, tubocurarine, metocurine and gallamine), the results obtained were highly variable. The EC_{50} values were observed to increase (by 9–366%, median 47%), to

decrease (by 52% for pancuronium) or to remain unaltered for these drugs in different animal species during moderate and severe hypothermia.

For another target, the EC_{50} for furosemide (frusemide) was increased. For morphine, an increased EC_{50} of 366% was observed and the affinity for the μ opioid receptor specifically was decreased by 448% at 30°C. However, opioid receptor affinity for the antagonist naloxone was unaltered. The observed effects on the γ -value were decreased (2%), unaltered or increased (by 5–15%, median 7%). Studies with isoprenaline, epinephrine (adrenaline) and dobutamine showed decreased EC_{50} values for the majority of the examined properties at different temperatures (13–88%, median 71%). E_{max} values did not show similarity for the investigated parameters at different temperatures (from –34% to +170%).

Clinical data (six units of analysis): For targets (such as acetylcholine receptors and cholinesterase) of neuromuscular agents (neostigmine, vecuronium and atracurium), the obtained results were also highly variable in humans. The EC_{50} was observed to decrease by 7% for vecuronium and the EC_{95} was observed to decrease by 13% for neostigmine. Other EC_{50} values for these targets were observed to remain unaltered during mild and moderate hypothermia. The observed effects on γ -values decreased (by 0.43–1.3 per degree Celsius; the maximal increase was 111%). The k_{e0} values were decreased and increased (by –0.023 to +0.1 min^{-1} per degree Celsius). For propofol, the EC_{50} values did not alter during moderate hypothermia.

2.2.1 Interpretation

Enzymatic Inactivation

One of the main pharmacodynamic parameters is the EC_{50} , which reflects receptor sensitivity to a particular agent. Impaired receptor sensitivity is expressed as an increased EC_{50} – a right shift of the concentration-effect curve.

For targets of neuromuscular-acting drugs, the results of studies that are conducted in humans only show unaltered (or not significantly decreased) EC_{50} values at hypothermic regimens up to 34°C. In animal species, these results show both increased and decreased EC_{50} values. The sensitivity of the neuromuscular junction depends on factors such as acetylcholinesterase activity and the sensitivity of the postjunctional membrane to the transmitter. Changes in these factors will result in an altered pharmacodynamic response. Acetylcholinesterase, for example, is an enzyme that exhibits temperature dependency, as is observed for cerebral membrane-bound acetylcholinesterase.^[81] Theoretically, if only acetyl-

cholinesterase activity was impaired during hypothermia, EC_{50} values for non-depolarizing drugs (e.g. pancuronium) would increase and EC_{50} values for acetylcholinesterase inhibitors (e.g. neostigmine) would decrease because of less acetylcholine inactivation by acetylcholinesterase. Results in the literature do not correspond with this theory, suggesting that impaired acetylcholinesterase activity is not the only contributing factor.

The sensitivity of cardiac catecholamine receptors to sympathomimetic drugs (epinephrine, isoprenaline and dobutamine) is increased (with a decreased EC_{50}) for cardiac contraction velocity, heart rate and cardiac oxygen consumption at the majority of examined temperatures. Results regarding the E_{max} are not generalizable, since they depend on the temperature and the investigated parameter. For isoprenaline only, an increased EC_{50} and an increased E_{max} were observed for all parameters at all hypothermic temperatures.

Increased sensitivity to cardioactive sympathomimetic drugs could be explained by reduced activity of the enzyme catechol-*O*-methyltransferase, which is responsible for degradation of catecholamines.^[79,82] The selectivity of dobutamine disappeared at hypothermic temperatures, resulting in increased α -adrenoceptor activity and thus increased vasoconstriction. Administration of sympathomimetics during hypothermia without dose adjustment could result in an increased effect.

Drug-Target Affinity

The affinity of morphine for μ opioid receptors (K_A) was observed to be decreased by 448% in an *in vitro* study in guinea pigs. μ Opioid receptors are responsible for supraspinal anaesthesia, respiratory depression and euphoria. The affinity of the antagonist (pA_2) naloxone for opioid receptors has been observed to be unaltered. This suggests that temperature affects binding of opioid receptor agonists and antagonists differently, as demonstrated by Puig et al.^[78] and Simantov et al.^[83] Thus a higher plasma concentration is required for morphine analgesia but not for naloxone if antagonism is required. The maximal effect of furosemide was delayed in rats. The maximal effect was at 5 minutes at 37°C, and the effect kept increasing for as long as 35 minutes at 30°C. The EC_{50} for the volume of urine excreted for furosemide was increased because of a reduced GFR. The volume of urine excreted was 40% at 30°C and 1.8% at 26°C of the normothermic value.^[65] Thus diuretic action with furosemide during hypothermia requires higher dosing in rats.

Onset and Recovery of the Effect

The onset of the effect and recovery of the effect depend on multiple factors such as the EC_{50} , the γ -value and the k_{e0}

Table V. Effect of hypothermia (HT) on pharmacodynamic (PD) parameters

Study	Species and model	Drug/agent	Thermic regimen	Relative difference in PD parameters in HT group vs NT group
Miller et al. ^[26]	Cat; <i>in vivo</i> (n = 18)	Pancuronium	Moderate and severe HT (39°C vs 34°C and 29°C)	EC ₅₀ decreased 52% at 29°C
Ham et al. ^[27]	Cat; <i>in vivo</i> (n = 16)	Tubocurarine	Moderate and severe HT (39°C vs 34°C and 28°C)	Time to E _{max} prolonged ~35% at 34°C and ~350% at 28°C (NP) ^a EC ₅₀ increased 30% at 34°C and 29% at 28°C (Total) recovery of twitch tension prolonged ~50% at 34°C and ~150% at 28°C (NP) ^a
Kondratiev et al. ^[38]	Rat; <i>in vivo</i> (n = 37)	Epinephrine (adrenaline)	Rewarming regimen from 13–37°C	EC ₅₀ decreased (NP)
Greven ^[65]	Rat; <i>in vivo</i> (n = 76)	Furosemide (frusemide)	Severe HT (37°C vs 30°C vs 26°C)	EC ₅₀ ^a increased E _{max} delayed 7-fold at 30°C
Horrow and Bartkowski ^[77]	Rat; <i>in vitro</i> (n = 5)	Tubocurarine	Severe HT (37°C vs 31°C and 25°C)	EC ₅₀ increased 47% at 31°C and 44% at 25°C γ-value increased 5% at 31°C and unaltered at 25°C
		Pancuronium	Severe HT (37°C vs 31°C and 25°C)	EC ₅₀ increased 9% at 31°C and decreased 2% (NS) at 25°C γ-value increased 15% at 31°C and decreased 2% at 25°C
		Metocurine	Severe HT (37°C vs 31°C and 25°C)	EC ₅₀ increased 73% at 25°C and 109% at 31°C γ-value unaltered at 31°C and increased 10% at 25°C
		Gallamine	Severe HT (37°C vs 31°C and 25°C)	EC ₅₀ increased 47% at 31°C and 75% at 25°C γ-value increased 7% at 31°C and decreased 10% at 25°C
Puig et al. ^[78]	Guinea pig; <i>in vitro</i> (n = NA)	Morphine	Severe HT (37°C vs 30°C)	EC ₅₀ increased 366% at 30°C γ-value decreased 21% at 30°C pA ₂ for opioid receptors for the antagonist naloxone unaltered K _A for μ opioid receptors for morphine decreased 448%
Riishede and Nielsen-Kudsk ^[79]	Rabbit; <i>in vitro</i> (n = 7)	Isoprenaline	Severe HT (37°C vs 22°C)	EC ₅₀ decreased 78%; E _{max} increased 63%; γ-value decreased 17% for cardiac contraction velocity EC ₅₀ decreased 76%; E _{max} unaltered; γ-value decreased 57% for heart rate frequency EC ₅₀ decreased 71%; E _{max} increased 62%; γ-value decreased 44% for cardiac oxygen consumption
	Rabbit; <i>in vitro</i> (n = 13)	Epinephrine	Severe HT (37°C vs 27°C and 22°C)	EC ₅₀ decreased 88% at 27°C and 85% at 22°C; E _{max} decreased 34% at 27°C and increased 21% at 22°C; γ-value decreased 24% at 27°C and 12% at 22°C for cardiac contraction velocity EC ₅₀ increased 17% at 27°C and decreased 13% at 22°C; E _{max} unaltered at 27°C and increased 75% at 22°C; γ-value increased 6% at 27°C and 752% at 22°C for heart rate frequency EC ₅₀ decreased 28% at 27°C and 42% at 22°C; E _{max} increased 75% at 27°C and 170% at 22°C; γ-value decreased 60% at 27°C and 47% at 22°C for cardiac oxygen consumption
		Dobutamine	Severe HT (37°C vs 27°C and 22°C)	EC ₅₀ increased 15% at 27°C and decreased 79% at 22°C; E _{max} decreased 24% at 27°C and 26% at 22°C;

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Table V. Contd

Study	Species and model	Drug/agent	Thermic regimen	Relative difference in PD parameters in HT group vs NT group
				<p>γ-value decreased 53% at 27°C and 56% at 22°C for cardiac contraction velocity</p> <p>EC₅₀ decreased 67% at 27°C and 74% at 22°C; E_{max} increased 18% at 27°C and 29% at 22°C; γ-value decreased 38% at 27°C and 47% at 22°C for heart rate frequency</p> <p>EC₅₀ decreased 46% at 27°C and 73% at 22°C; E_{max} increased 49% at 27°C and 64% at 22°C; γ-value decreased 38% at 27°C and 34% at 22°C for cardiac oxygen consumption</p>
Heier et al. ^[32]	Human; <i>in vivo</i> (n = 7)	Neostigmine	Moderate HT (37°C vs 34°C)	<p>Time to E_{max} T1 prolonged 10%</p> <p>Duration of action unaltered</p> <p>EC₉₅ decreased 13% (NS)</p>
	Human; <i>in vivo</i> (n = 10)	Vecuronium	Moderate HT (36.8°C vs 34.4°C)	<p>EC₅₀ decreased 7% (NS)</p> <p>k_{e0} increased 0.1 min⁻¹ per °C (NS)</p> <p>γ-value increased 30% [NS]</p>
Leslie et al. ^[62]	Human; <i>in vivo</i> (n = 6)	Atracurium	Moderate HT (37°C vs 34°C)	<p>Time to recovery of T1 to 10% of its control height prolonged 60%</p> <p>Time for T1 to recover 25–75% of control unaltered</p>
Leslie et al. ^[35]	Human; <i>in vivo</i> (n = 40)	Propofol	Moderate HT (37°C vs 34°C)	<p>γ-value increased 111%^a</p> <p>EC₅₀ unaltered</p>
Caldwell et al. ^[63]	Human; <i>in vivo</i> (n = 12)	Vecuronium	Mild and moderate HT (>37°C, 36–36.9°C, 35–35.9°C and <35°C)	<p>Duration of effect prolonged (NP)</p> <p>k_{e0} decreased 0.023 min⁻¹ per °C</p> <p>EC₅₀ unaltered</p> <p>γ-value increased 0.43 per °C</p>
Heier et al. ^[80]	Human; <i>in vivo</i> (n = 20)	Vecuronium	Moderate HT (36.5°C vs 34.5°C)	<p>Time of onset unaltered</p> <p>Duration of effect prolonged 121%</p> <p>Time to recover prolonged, e.g. recovery index (T1 = 25% to T1 = 75% of control) prolonged by 238%</p>

a Data extracted or estimated from a figure or graph.

γ -value = shape factor or Hill factor (steepness of concentration-effect curve); EC_n = concentration giving n% of the maximum effect; E_{max} = maximum effect; K_A = dissociation constant; k_{e0} = rate constant for drug equilibration between plasma and the effect site; NA = data not available; NP = data not provided by authors; NS = data not significant; NT = normothermia; pA₂ = negative log of the antagonist concentration that produces a 2-fold shift of the dose-response curve; T1 = first twitch.

for the particular drug and target. The γ -value represents the steepness of the concentration-effect curve, which reflects the magnitude of the effect with an increasing dose. A decreased EC₅₀, an increased γ -value and an increased k_{e0} favour a rapid onset of the effect and delayed recovery, causing an increased duration of action. For vecuronium, the k_{e0} value for vecuronium was increased and decreased in two different studies. In both studies, the γ -value was observed to be increased.^[80,84]

The influence of hypothermia on the pharmacodynamic response therefore depends not only on drug-target interaction

on the basis of affinity but also on alterations in subsequent (enzymatic) processes, which are responsible for activation or degradation of, for example, neurotransmitters such as acetylcholinesterase and catechol-O-methyltransferase. It also depends on other local characteristics at the drug effect site, such as membrane fluidity and the mechanical contractile response.

Pharmacokinetic and pharmacodynamic parameters may alter during hypothermia in comparison with normothermia. The direction and magnitude of the change in pharmacokinetic/pharmacodynamic parameters is highly variable between

drugs and individual parameters. The most striking effect is the impaired clearance during hypothermia. These alterations in pharmacokinetic/pharmacodynamic parameters will require dose adjustment for many drugs during therapeutic hypothermia to prevent toxicity and therapy failure. Clinical studies are currently being performed in hypothermic neonates at our centre in an attempt to develop population pharmacokinetic/pharmacodynamic models.

2.3 Rewarming

After the hypothermic phase, patients have to be rewarmed slowly until normothermia is reached. During this period, pharmacokinetic and pharmacodynamic parameters will alter again until normothermia is reached. Clearance, for example, may increase. A theoretical time-course model of CYP activity during hypothermia and rewarming was provided by Tortorici et al.^[66] In a cardiac-arrest rat model, drug metabolism normalized after rewarming, because of attenuation of the cardiac-arrest-mediated downregulation by the hypothermia.^[85]

During the transition from hypothermia to normothermia, the affinity of (accumulated) morphine for the μ opioid receptor increases. This may result in increased supraspinal anaesthesia but also in more respiratory depression. Without respiratory support, the consequences could be severe. When the V_d decreases as a consequence of raising temperature, this could result in toxic concentrations but also in therapy failure if efficacy depends on the tissue concentration rather than the concentration in plasma, as could occur with antibacterials and cytotoxic agents. In contrast, when the V_d increases, this could result in therapy failure. In pigs, the plasma concentration of fentanyl was increased until 6 hours after reaching normothermia.^[52]

2.4 Limitations

This systematic review summarizes the available evidence on the effect of therapeutic hypothermia on individual pharmacokinetic/pharmacodynamic parameters. Studies that determined pharmacokinetic or pharmacodynamic parameters during cardiopulmonary bypass (CPB) were excluded from the search. CPB may have significant effects on pharmacokinetics and pharmacodynamics because of altered haemodynamics due to haemodilution, altered regional blood flow and blood pressure, shifts in fluids and electrolytes, and possible uptake of the drug by the bypass circuit.^[86,87] Moreover, such consequences in the context of CPB are a result of both CPB

and hypothermia, and cannot always be ascribed to hypothermia only.

Studies concerning the pharmacokinetics and pharmacodynamics of volatile agents during hypothermia were also excluded since these agents have pharmacokinetic and pharmacodynamic profiles different from those of non-volatile agents. Volatile agents such as isoflurane and sevoflurane are mainly excreted unchanged by the lungs.^[88,89] Besides alterations in distribution and excretion, multiple factors contribute to their altered pharmacokinetics and pharmacodynamics, such as tissue solubility.^[90]

One might wonder whether the investigators of the studies included in the review chose the particular investigated drug because of an *a priori* expectation that hypothermia would affect the pharmacokinetics/pharmacodynamics of that drug. It is still unknown whether these results can be extrapolated to drugs other than the investigated ones (e.g. paracetamol [acetaminophen]).

Different hypothermic regimens were applied in the studies included in this review. Our goal was to provide an overview of what basically happens to pharmacokinetic/pharmacodynamic parameters during hypothermia and to provide an overview of (possible) contributing underlying mechanisms. Therefore, we chose to include studies involving various different hypothermic regimens. From a physiological and physicochemical standpoint, the magnitude of the effect on pharmacokinetic/pharmacodynamic parameters will increase when temperature reduction increases. Different hypothermic regimens require different dose adjustment recommendations.

The majority of the studies included in this review (74%) were conducted in animals. The effects of hypothermia on pharmacokinetic/pharmacodynamic parameters cannot be extrapolated to humans without application of an appropriate scaling technique, because of interspecies variability. According to traditional allometric scaling, many physiological processes tend to obey a power function. The exponents are 0.75 for metabolic processes and 1.0 for physiological volumes. Considering pharmacodynamics, the capacity and sensitivity parameters (the E_{max} and EC_{50}) tend to be similar across species. For other pharmacodynamic parameters, allometric scaling should be applied.^[91] Different studies have investigated this by using different techniques.^[91-95] In some studies, estimations of 'correction factors' for the normalization of, for example, CL_R in different species were provided. Anyway, data derived from animal studies can provide an indication of the effect of hypothermia, which facilitates the development of mechanism-based pharmacokinetic/pharmacodynamic models. For example, studies regarding the effect of hypothermia on

CL_{int} are conducted with animal tissue only. These data provide an understanding of the underlying mechanism that alters clearance during hypothermia.

3. Conclusions

During hypothermia, pharmacokinetic parameters alter. Impaired clearance is the most striking effect, resulting in drug and sometimes metabolite accumulation. On the basis of impaired clearance, dosages should be decreased considerably, especially for drugs with a low therapeutic index. Hypothetically, high-clearance compounds are affected more than low-clearance compounds because of the additional effect of impaired hepatic blood flow. The V_d alters too in a relatively predictable manner for acids and bases, according to the pH-partitioning hypothesis, and could therefore result in toxicity or therapy failure. Changed absorption is another complicating factor. Pharmacodynamic parameters also alter, depending on the hypothermic regimen, drug target location, pharmacological mechanism and metabolic pathway of inactivation. The pharmacological response changes when target sensitivity changes. Rewarming patients to normothermia can also result in toxicity or subtherapeutic treatment. The integrated effect of hypothermia on pharmacokinetic and pharmacodynamic properties of individual drugs is not always predictable. Therefore, therapeutic drug monitoring is currently considered essential for drugs with a low therapeutic index, drugs with active metabolites, high-clearance compounds and drugs that are inactivated by enzymes at the site of the effect. From a physiological and physicochemical standpoint, the magnitude of the effect on pharmacokinetic/pharmacodynamic parameters will increase when temperature reduction increases. Different hypothermic regimens require different dose adjustment recommendations. Further clinical pharmacokinetic/pharmacodynamic studies are necessary for development of substantiated dose regimens to avoid toxicity and therapy failure in hypothermic patients.

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