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Therapeutic Mild Hypothermia and the Pharmacokinetics of Drugs in Trauma Brain Injury (TBI) Patients with a Focus on Sedation, Anticonvulsant and Antibiotic Therapy

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Abstract: *Background*: Therapeutic hypothermia may alter both the pharmacokinetic (PK) and dynamics (PD) of the commonly used drugs in critical care. To achieve maximum benefit, medication dosage and schedules should be optimized.

Objective: To review the existing scientific evidence showing the effect of therapeutic hypothermia on the pharmacokinetics of drugs commonly used in the care of patients after Trauma Brain Injury (TBI); particularly including sedatives, anticonvulsants and antibiotics.

Data Sources: Computerized searches of OVID MEDLINE, OVID EMBASE, Cochrane Clinical Trials Register to August 2013 and hand searching of references of retrieved articles and proceedings of meetings; associated reference lists; and articles identified by experts in the field.

Study Selection: Inclusion criteria were as follows: a) population- humans or animals undergoing therapeutic hypothermia b) design-prospective, randomized controlled trial, c) intervention-hypothermia; measurement of PD and PK of different drugs.

Data Extraction: A data extraction form was used and authors (CB & SP) reviewed all trials.

Data Synthesis: We reviewed 30 trials that documented changes in PD and PK of sedatives (propofol and midazolam), opioids (fentanyl, remifentanil, alfentil and morphine), anticonvulsants (phenytoin) and antibiotics (aminoglycosides) conducted in human or animal models undergoing therapeutic hypothermia.

Conclusion: Data show that therapeutic hypothermia significantly alters the pharmacokinetics of commonly used agents. Particular care should be taken to reduce sedatives once target temperature is reached. Further clinical studies are required to clarify the effect of hypothermia on the PD and PK of therapeutic agents to optimize the benefits of therapeutic hypothermia in the treatment of TBI patients.

Keywords: Trauma brain injury (TBI), therapeutic hypothermia (TH), pharmacokinetics (PK), pharmacodynamics (PD).

INTRODUCTION

Understanding the effects of hypothermia on drug metabolism is crucial when optimizing its application and will increase the quality of patient care. Particularly as critical care patients receive, on average, twice the number of medications compared with patients on general medical wards [1] and this increases the possibility of drug interactions and toxicity. Most of the drugs used in critical care are metabolized by the liver and the Cytochrome P450 system (CYP450). The CYP450 is a large and diverse group of enzymes belonging to the superfamily of proteins containing a heme cofactor. They form part of multi-component ubiquitous transfer chains and in the liver are critical to metabolizing a wide variety of drugs and toxic compounds [2].

Therapeutic hypothermia (TH) is a promising intervention in the management of a number of acute brain injury syndromes including; traumatic brain injury [3-5], following cardiac arrest [6-8], ischemic stroke [9], neonatal asphyxia [10], subarachnoid haemorrhage and during some neurosurgical procedures. After cardiac arrest, with an initial rhythm of ventricular fibrillation, the treatment is now recommended by NICE, the European Resuscitation Council and the American Heart Association [8]. The data on effectiveness of TH following traumatic brain injury (TBI) is

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less robust, due largely to small, poor quality trials [3, 11-15].

Key elements for the successful use of TH are awareness and proper management of the physiological consequences and side-effects of treatment. Untreated or poorly managed complications may negate any potential benefits of treatment [2, 11, 12, 16].

Since most enzymatic processes exhibit temperature dependency, it is reasonable to expect therapeutic hypothermia will cause alterations in pharmacokinetic and dynamic (PK and PD) parameters, leading to an increased risk of drug toxicity or therapy failure [17]. Generalisable knowledge about the effect of therapeutic hypothermia on pharmacokinetics and pharmacodynamics will lead to more appropriate dosing and effective therapy [2, 18].

SUMMARY OF POTENTIAL EFFECTS OF HYPOTHERMIA

Hypothermia modulates many different post acute brain injury processes, some of which may be responsible for secondary brain damage. For example, hypothermia reduces the pro-inflammatory response and can lead to an improvement in brain tolerance of ischemia, hypoperfusion and reperfusion damage. It is also associated with a decrease in free radicals release and a reduced activation of the apoptotic pathway. Historically, reduction of the systemic and cerebral metabolic rate through therapeutic hypothermia, even when coupled with mild metabolic acidosis, is considered one of the most important mechanisms to reduce damage and is still regarded as such today [18, 19]. TH also causes a reduction in blood-brain barrier disruption and a decrease in vascular permeability which reduces the formation of edema [2].

Hypothermia is however, characterized by several important side-effects, and failure to adequately manage them is believed to be responsible for the failure to replicate the effectiveness of TH in experimental studies in clinical trials in TBI. The relevant side effects of therapeutic hypothermia are summarized in Table **1**.

Table 1. Common Side Effects of Therapeutic Therapeutic Hypothermia

- Shivering
- Hyperglycemia and decreased insulin sensitivity
- Depletion of electrolyte levels: hypoK^+, hypoMg^{++}, hypoPhosphatemia
- Decreased metabolic rate, pO_2 and pCO_2 level and increase in pH
- Hemodynamic instability
- Mild coagulopathy
- Rising infection risk : VAP, surgical wound infection, catheter-related infections.
- Altered drug pharmacokinetics (PK) and pharmacodynamics (PD)
- Mild rise in free fatty acids, ketones, lactate, glycerol, amylase and liver enzymes

OBJECTIVES OF THIS PAPER

The objective of this paper is to review the existing scientific evidence showing the effect of therapeutic hypothermia on the pharmacokinetics of drugs commonly used in the care of patients after Trauma Brain Injury (TBI); particularly including sedatives, anticonvulsants and antibiotics.

METHODS

Data Sources

Computerized searches of OVID MEDLINE, OVID EMBASE, Cochrane Clinical Trials Register to August 2013 and hand searching of references of retrieved articles and proceedings of meetings; associated reference lists; and articles identified by experts in the field.

Study Selection

Inclusion criteria were as follows: a) population- humans or animals undergoing therapeutic hypothermia b) design-prospective, randomized controlled trial, c) intervention-hypothermia; measurement of PD and PK of different drugs. Search terms included: Traumatic Brain Injury; Head Injury; Therapeutic hypothermia; Pharmacokinetic(s), clinical and population; Pharmacodynamic(s), clinical and population; half life; drug clearance.

Data Extraction

A data extraction form was used and authors (CB & SP) reviewed all trials.

Data Synthesis

We reviewed 30 trials that documented changes in PD and PK of sedatives (propofol and midazolam), opioids (fentanyl, remifentanil, alfentil and morphine), anticonvulsants (phenytoin) and antibiotics (aminoglycosides) conducted in human or animal models undergoing therapeutic hypothermia.

RESULTS

Cytochrome P450 Enzyme System

There are few studies conducted to specifically clarify the effect of hypothermia on the disposition and response of medications. Tables **2** and **3**. Nevertheless, some small studies, on animals and humans, have highlighted the key role of CYP450 activity variation in metabolising drugs in mild-to-moderate hypothermia [2, 20, 21]. Collectively, these studies have shown that hypothermia decreases the clearance of drugs through a reduction in hepatic elimination.

Studies conducted on humans during anaesthesia have previously reported an increased duration of action of vecuronium during mild hypothermia and a decreased rate of recovery [22, 23]. The increased duration of action cannot be explained by PD factors, as TH has been reported to not alter the plasma concentration–effect mechanism, and it is therefore likely due to altered distribution and elimination (PK variables). Fukuoka *et al.* have shown a five-fold increase in plasma concentrations of midazolam when the core temperature of brain-injured patients was maintained <35°C confirming that hypothermia decreases the clearance (CL) of certain hepatically eliminated drugs [20].

Tortorici *et al*. found that mild to moderate hypothermia decreases the systemic clearance of CYP450-metabolized drugs between 7 and 22% per degree Celsius below 37°C.

Table 2. Effect of Therapeutic Hypothermia on Drugs PK

Study	Species and Model	Drug	Thermic Regimen	PK Parameter	
				CL	Vd
Tortorici *et al.*	Rat; *in vitro* (n=8)	Chlorzoxazone	Severe HT (37°C *vs* 30°C)	Km increased 116% Vmax unaltered CLint, of CYP2E1 decreased 44%	
	Rat; *in vivo* (n=6)	Chlorzoxazone	Severe HT (37°C *vs* 30°C)	CL decreased 54% ke decreased 66% Urinary metabolite excretion decreased 76%	Increased 27%
Leslie *et al.*	Human; *in vivo* (n=6)	Propofol	Moderate HT (37°C *vs* 34°C)	CL decreased 25% (NS)	-
Fukoka *et al.*	Human; *in vivo* (n=15)	Midazolam	Moderate HT (37°C *vs* 32°-34°C)	CL decreased 99.4%	Increased 83%
Bansinath *et al.*	Dog; *in vivo* (n=18)	Morphine	Severe HT (37°C *vs* 30°C)	CL decreased 70%	Decreased 33%
Roka *et al.*	Human; *in vivo* (n=16)	Morphine	Moderate HT (37°C *vs* 32°-34°C)	CL decreased 22%	-
Fritz *et al.*	Pig; *in vitro* (n=6)	Fentanyl	Severe HT (37.7°C *vs* 31.6°C)	Conversion rate of CYP3A4 decreased 31% at 32°C and 56% at 26°C)	-
Iida *et al.*	Human; *in vivo* (n=14)	Phenytoin	Moderate HT (37°C *vs* 34°C)	CL decreased 67% ke decreased 50% Metabolite plasma concentration decreased (NP)	Unaltered
Koren *et al.*	Pig; *in vivo* (n=7)	Gentamicin	Severe HT (37°C *vs* 29°C)	CL decreased 51% ke decreased 27%	Decreased 32%
Satas *et al.*	Pig; *in vivo* (n=16)	Gentamicin	Moderate HT (39°C *vs* 35°C)	CLr unaltered	-

Impaired clearance is the most striking effect of TH, resulting in drug and metabolite accumulation with a subsequent reduction in TD50 (median toxic dose) and therapeutic index of most commonly used drugs following TBI. This can lead to increased side effects of therapeutic hypothermia and reducing its potential benefits [18].

Hepatic microsomal cytochrome P450 3A4 (CYP3A) activity tested *in vitro* by ethylmorphine N-demethylation was shown to be temperature dependent. Hypothermia induced a strong temperature-dependent reduction in hepatic CYP3A activity (48% *vs* 32%) [17].

The most commonly used drugs in patients after TBI are sedatives, hypnotics, analgesics, anti-convulsants and antibiotics.

Sedatives: Propofol and Midazolam

Propofol is commonly used in intensive care medicine and has a high hepatic extraction ratio. Its PK during mild hypothermia was studied by Leslie *et al*. in two different studies on healthy volunteers and on neurosurgical patients [24, 25]. Propofol blood concentration increased by approximately 28% and the inter-compartmental clearances decreased at 34°C compared with 37°C. Total Body Clearance (TBC), central and compartmental distribution volumes (Vd) are not significantly modified by temperature. Hepatic blood flow decreased during propofol administration but no significant change in hepatic blood flow was caused by hypothermia. Hypothermia significantly alters the concentration present at the drug effect site, decreasing propofol partitioning between the central and peripheral compartments, and intercompartmental clearances are decreased in the presence of hypothermia [2, 24, 26]. In an RCT conducted in 40 neurosurgical patients, Leslie *et al*. compared Propofol blood levels and bispectral index (BIS) value at the CP50-awake of propofol at 34°C. Propofol concentration, but not the core temperature, predicted the responsiveness to command and noted that core temperature did not alter the relationship between BIS and response to command [25]. Thus BIS monitoring during Propofol anaesthesia and or sedation remains reliable during TH.

Midazolam is a frequently used benzodiazepine in ICU with sedative and anticonvulsant properties. A 5-fold increase in blood concentration due to a nearly 100% decrease in systemic clearance (CL) during hypothermia was reported in patients following TBI, when administered by a continuous infusion [20]. These data are however, challenged by two recent, small observational studies [26, 27].

Opioid Analgesics: Fentanyl, Remifentanil, Alfentanil and Morphine

Fentanyl is a commonly used opioid analgesic in ICU. It is characterized by a high hepatic extraction ratio and a large volume of distribution. Its PK during TH has been extensively studied in experimental animal models. Two of these studies showed a consistent increase in Fentanyl blood concentration during hypothermia, persisting for more than 6 hours after rewarming. Increased blood concentration can be explained by two mechanisms: reduced bio-transformation rates and CL coupled with a reduced volume of distribution of Fentanyl. The reduced bio-transformation can be partly attributed to a reduction in organ perfusion/ blood flow and

Table 3. Hypothermia Specific Effects on Various Commonly Used Drugs

Medication	Hypothermia Effect	Impact	Reference
Opioid			
Remifentanil[1] Fentanyl[3]	↓ Clearance ↓ Volume of distribution	↓ Dosage (30 %)[2]	[17, 30, 44]
Morphine[3]	↑ Plasma concentration ↑ Half-life of elimination	↓ Dosage (30 %) Slower titration	[36]
Sedation			
Propofol[1]	↑ Plasma concentration	↓ Dosage (30 %)	[24, 44]
Midazolam[1]	↑ Plasma concentration ↑ Volume of distribution ↓ Clearance	↓ Dosage	[20]
Neuromuscular Blocker			
Vecuronium[1] Rocuronium[1]	↓ Clearance ↑ Time before effect	↓ Dosage (30 %) Monitor	[45, 46]
Atracurium[1]	↓ Clearance	Delayed intubation	[47, 48]
Vasoactive Medication			
Glyceryl trinitrate[1]	↓ Clearance	↓ Dosing after effect	[49]
Anticonvulsants			
phenytoin[1]	↓ Clearance ↓ Plasma concentrations of total and unbound drug	↓ Dosage Adjust according to serum concentration measurements	[39]

[1]Experiments on humans.
[2]Recommendation concerning maintenance therapy.
[3]Experiments on animals.

partly to a decreased cytochrome activity. End organ arterial blood flows, such as total hepatic blood flow, are markedly decreased by hypothermia. However, hepatic arterial blood flow is the only organ perfusion to remain unaltered.

The blood concentration of fentanyl increases during therapeutic hypothermia and may contribute to secondary brain damage due to three mechanisms; fentanyl is not particularly effective at reducing the stress response due to TH, furthermore it fails to blunt post-traumatic excitotoxicity and it may also reduce CBF. In patients with partial complex epilepsy fentanyl can induce seizures even in the "healthy temporal lobe" [29]. Additionally, two different studies have demonstrated that hypothermia in fentanyl-anesthetized rats was detrimental in traumatic brain injury and cerebral ischemia [29].

PK studies have been conducted in humans during mild to moderate hypothermia during cardiopulmonary bypass (CPB) surgery, in both adult and pediatric patients. They confirmed that Fentanyl metabolism, by the cytochrome system, is severely impaired [17, 28] (Fig. **1**). Most of these studies were performed during CBP, making it difficult to determine whether changes in PK were the result of hypothermia itself or due to extracorporeal circulation.

New studies are required to clarify the role of fentanyl administration in influencing neurological outcome during therapeutic hypothermia therapy.

Remifentanil is a potent μ-agonist at the opioid receptor. Its PK is different from other opiates because it has a very short half-time and its elimination is due to nonspecific blood and tissue esterases. All the recent studies on remifentanil in hypothermia have been conducted on patients undergoing CPB [30, 31]. Remifentanil PK is modified during hypothermic CPB by hemodilution, altered protein binding, uptake (adsorption) of drugs by the circuit and isolation of lungs from the circulation. Michelsen *et al.* [30] showed a decrease in the elimination/ clearance (CLe) during hypothermia: there is a proportional decrease of 6.37% in CLe with each degree Celsius decrease in temperature below 37°C, likely due to decreased enzyme activity in blood and tissue with decreasing temperature.

Alfentanil is a μ opioid receptor agonist frequently used in anesthetic practice and in ICU. Some pharmacokinetics parameters, including the steady-state volume of distribution, are similar to remifentanil with the substantial difference that alfentanil has a significantly reduced central clearance. Pharmacodynamically both require a similar time for equilibrium to be reached between blood and effect-site concentration, but Alfentanil is 19 times less potent than remifentanil [32]. Alfentanil administration during hypothermia has been demonstrated useful in reducing vasoconstriction and shivering thresholds linearly as a function of dose [33]. No *critical care* pharmacokinetic studies on alfentanil administration during hypothermia treatment in animals or humans have been conducted. Petros

et al. have studied Alfentanil PK after therapeutic hypothermia in three groups of patients, all undergoing thoracic surgery: two groups of patients underwent cardiac surgery with hypothermia (26.3°C and 33.9°C) CPB technique and a group of control patients underwent lateral thoracotomy for pulmonary diseases. The mean temperature of each group at the end of CPB did not differ significantly when alfentanil was administered. There were no significant differences in terms of Clearance and in distribution volumes [34].

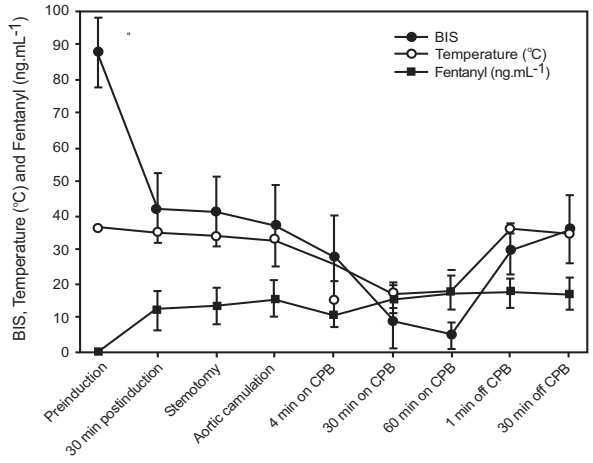

Fig. (1). Changes in BIS, plasma fentanyl, and nasopharyngeal temperature. Data are mean ± SD. Data are based on n=15 except preinduction (n=5). BIS, bispectral index. CPB, cardiopulmonary bypass. For BIS preinduction to 30 minutes postinduction (p= 0.02), aortic cannulation to 30 minutes on CPB (p< 0.001), and 60 minutes on CPB to 1 minute off CPB (p<0.001). Kussman BD, Zurakowski D, Sullivan L, *et al*: Evaluation of plasma fentanyl concentrations in infants during cardiopulmonary bypass with low-volume circuits. J Cardiothorac Vasc Anesth 2005; 19: 316-321.

Morphine PK and cardiovascular effects have been studied in animals and humans in hypothermic conditions. Two studies performed on isoflurane anaesthetised dogs highlighted the key morphine PK variation during hypothermia when 1 mg/kg, was administered intravenously. At 30°C dogs showed significantly higher levels of morphine both in plasma and cerebrospinal fluid coupled with a reduction in total body Clearance and increased main residence time (MRT). Body temperature did not affect the $t_{1/2}$alpha, while $t_{1/2}$beta was increased. The distribution volume at steady state was decreased [35, 36].

Hypothermia also influences Morphine PD; a study on a pig ileum preparation has demonstrated that decreasing body temperature to 30 °C can reduce Morphine potency when compared to 37°C. This reduction in potency may be related to a reduction in receptor affinity, demonstrated by a six-fold increase in the dissociation constant of Morphine for the μ-receptor [37]. Hypothermia increases Morphine plasma level and globally reduces its potency [2]. A randomized controlled study in neonates of moderate whole-body mild hypothermia after perinatal asphyxia has confirmed that serum Morphine concentrations after continuous infusion are higher in hypothermia-treated infants than in the control group despite a similar rate of infusion and cumulative doses in both groups. Morphine clearance was reduced in both groups. Contingent toxic effects related to elevated serum drug levels remain to be clarified [38].

Caution should be exercised when translating cardiopulmonary bypass data to adult critical care because the steady-state volume of distribution (Vss) increases with the institution of CPB because of hemodilution(30), substantially altering PK.

Anticonvulsant: Phenytoin

Phenytoin is one of the most commonly used anticonvulsant drugs in ICU. It's hepatic clearance depends on both the unbound drug fraction concentration and on the activity rate of hepatic enzymes. Hepatic blood flow variation has little influence on phenytoin elimination clearance. The fraction bound to albumin is 90% and Phenytoin activity is dependant on its unbound drug fraction. The unbound fraction has been shown to be increased in critically ill patients and is inversely related to serum albumin concentration. Phenytoin hepatic elimination is principally due to the hydroxylation to 5-p-HPPH through a reaction catalized by CYP2C9 and CYP2C19. The elimination kinetics of this reaction can saturate at the therapeutic blood concentration of phenytoin and is governed by the Michaelis-Menten formula. It is therefore mandatory to use strict blood level monitoring to guided therapy.

Phenytoin metabolism is influenced by several drugs, such as amiodarone, midazolam, antibiotics, vecuronium and barbiturates. The effect of mild hypothermia on phenytoin in patients following TBI has been examined by Iida *et al*. [39] who found that hypothermia significantly increased the plasma concentrations of total and unbound phenytoin. Moreover TH was able to reduce the elimination constant (ke) and elimination clearance by 50% and 67% respectively; additionally the concentration of it's major metabolite 5-p-HPPT was reduced, suggesting an inhibition in phenytoin's metabolism.

Our own data (Edinburgh, unpublished data) show hypothermia is associated with a significant effect on the corrected plasma phenytoin concentration with time. Corrected phenytoin levels were available on 15 patients, 8 hypothermia and 7 controls (enrolled in the Eurotherm3235Trial). Median sampling time was 4 days (range 3 to 10 days) and 5 days (range 4 to 10 days) for hypothermia *vs* control respectively, p=0.336. In the hypothermia group corrected phenytoin concentration increased with time from 13.0 ± 1.4 mg/l on day 1 to 15.5 ± 2.2 mg/l on day 8. Conversely in the control group corrected phenytoin concentration fell from 18.4 ± 2.4 mg/l to 10.2 ± 1.8 mg/l over the same interval. Two way ANOVA revelled a significant effect of treatment allocation on phenytoin levels, p<0.001. Pair wise multiple comparison indicated a significant interaction between time and treatment on days 1, 5, 7 and 10 of admission, p<0.05 (Fig. **2**).

Antibiotics

Hypothermia has been demonstrated to inhibit leukocyte migration and phagocytosis and decreases the synthesis of proinflammatory cytokines. The suppression of inflammation is considered one of the most important

protective mechanisms of hypothermia on injured brain, but may also lead to an increased risk of infection [2].

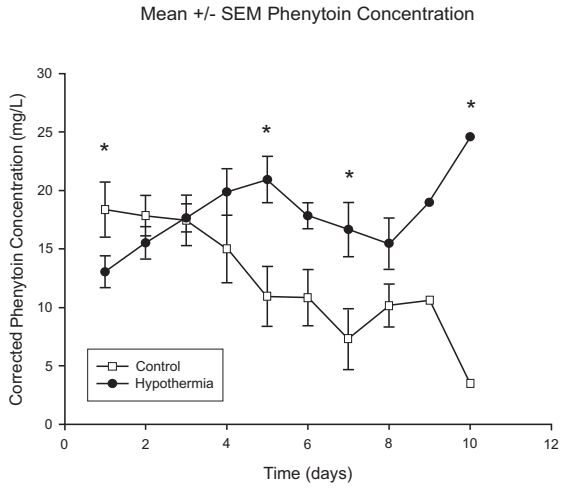

Fig. (2). Phenytoin pharmacokinetics in properly and prospectively randomized patients to hypothermia or normothermia [50].

Few PK studies have been conducted on antibiotics during therapeutic hypothermia. However, some studies have assessed the PK of aminoglycosides, such as gentamicin and netilmicin, in animals and humans [17, 40, 41]. Gentamicin is almost completely excreted renally and is unchanged. It has a nephrotoxic and ototoxic effect and because of this, needs strict monitoring of blood levels. Two studies in piglet models evaluated the PK of gentamicin during mild hypothemia. Koren *et al*. [17] found that this antibiotic, administrated by bolus at 29°C, results in an increase in serum concentration, prolonged elimination half-time and reduced total body clearance. The volume of distribution and the volume of the central compartment seem to be significantly decreased by TH (Fig. **3**). The authors reported

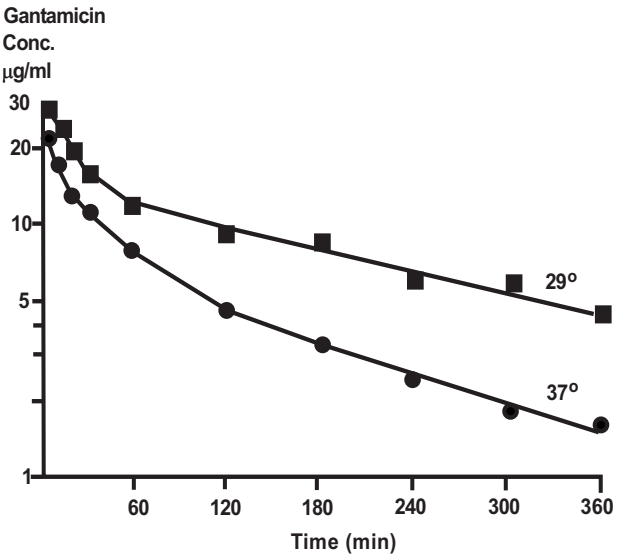

Fig. (3). Concentration-time curve of gentamicin given intravenously as a bolus of 5 mg/kg during normothermia and hypothermia (29°C). Koren G, Barker C, Bohn D *et al*. Influence of hypothermia on the pharmacokinetics of gentamycin and the theophylline in piglets. Crit Care Med1985; 13(10): 844-7.

a reduction in cardiac output during the induction of hypothermia in a temperature-dependent fashion, which may be responsible for a decrease in glomerular filtration rate [17]. A recent retrospective study examining 55 infants with hypoxic-ischemic encephalopathy treated with 72h duration of mild hypothermia (defined as 32-35°C) has shown that therapeutic hypothermia did not affect the clearance of gentamicin. Impaired renal function however, is strongly associated with serum gentamicin concentrations [41]. However, gentamicin clearance is decreased in neonates with HIE treated with hypothermia by up to 25% [42] compared with previous reports in non-asphyxiated normothermic full-term neonates. A prolonged 36-hour dosing interval will be needed to achieve target gentamicin trough concentrations in this population [43]. Because hypothermia may increase the risk of infections, further studies are required to clarify the effect of hypothermia on the PK and PD of anti-infectives.

CONCLUSIONS

Mild to moderate hypothermia can cause a reduction in clearance and an increase in drug plasma concentration and this may cause harm and limit the benefits of this promising therapy. Further clinical pharmacokinetic and pharmacodynamic studies are essential for the development of substantiated dose regimens during therapeutic hypothermia to avoid toxicity and reduce the risk of therapy failure. Reducing the infusion rates of morphine, fentanyl, and propofol during therapeutic hypothermia is encouraged.

CONFLICT OF INTEREST

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

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