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Pharmacokinetics during therapeutic hypothermia for neonatal hypoxic ischemic encephalopathy: a literature review

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ABSTRACT

Background Neonatal hypoxic ischemic encephalopathy, brain damage sustained as a result of perinatal asphyxia, can lead to severe neurodevelopmental disability or mortality. Hypothermia is at present the only proven neuroprotective intervention. During hypothermia, the neonate may need a variety of drugs with their specific pharmacokinetic profile. The aim of this paper is to determine the effect that hypothermia for neonates suffering from hypoxic ischemic encephalopathy has on the pharmacokinetics and to what extent dosing regimens need adjustments.

Method A systematic search was performed on Pubmed, Embase and Cochrane library of literature published between 2000 and January 2020 using a combination of the following search terms; therapeutic hypothermia, neonate, hypoxic ischemic encephalopathy and pharmacokinetics. Titles and abstracts were screened, and inclusion/exclusion criteria were applied. Finally, relevant full-texts were read, and secondary inclusion was applied on the identified articles.

Results A total of 380 articles were retrieved, and 34 articles included after application of inclusion/exclusion criteria and removal of duplicates. The resulting articles were sorted into drug group and discussed according to pharmacokinetic parameters (absorption, distribution, metabolism, excretion). Eleven (11) out of 34 studies demonstrated a significant decrease in clearance as high as 46% during the hypothermic period. A comparison of the recommended dosing regimen as suggested in the articles was made with the guidelines as stated in the Dutch paediatric formulary.

Conclusion Depending on the drug-specific disposition characteristics, therapeutic hypothermia in neonates with hypoxic ischemic encephalopathy affects pharmacokinetics.

What's known

- Therapeutic hypothermia has a neuroprotective effect for neonates with hypoxic ischemic hypothermia.
- Hypoxic ischemic asphyxia and lowering the core body temperature has impact on the pharmacokinetics of drugs administered during this period, up to the level that dosing regimens for these neonates should be adapted.

What's new

- This literature review provides an updated overview on pharmacokinetics and gives a clear overview of the research reported from January 2000 until January 2020.

INTRODUCTION

Neonatal hypoxic ischemic encephalopathy (HIE), brain damage sustained as a result of perinatal asphyxia, occurs in 1.5 out of 1000 births[1] and can lead to severe neurodevelopmental disability or mortality in respectively 24.9% and 34.1% of cases[2]. Perinatal asphyxia is a condition characterised by a persistently low APGAR-score (≤5) assessed at 5 and 10 minutes after birth, or metabolic acidosis, defined as a pH of < 7.0 and/or base deficit of ≥ 16 mmol/L, measured by analysing the blood in the foetal umbilical artery within 1 hour after birth[3,4]. The severity of the HIE can be categorised by the Sarnat score into mild, moderate and severe brain injury based on the abnormality of level of consciousness, spontaneous activity, posture, tone, primitive reflexes and autonomic function[5]. The Thompson score is a different scoring system that uses similar criteria to Sarnat but also includes the presence of seizures and fontanelle tension, the resulting score of which provides prognostic value and quantifies HIE [6].

Hypothermia is at present the only proven effective intervention for moderate and severe HIE. It significantly reduces the mortality by 8.8% and severe morbidity by 15.4% (relative risk = 0.75; number needed to treat = 7)[2]. In its current approach, therapeutic hypothermia (TH) aims to cool the body temperature of the neonate to 33.5˚C for the duration of 72 hours within 6 hours after birth, and a subsequently gradual rewarming at a rate of 0.3-0.5˚C per hour[7–10]. According to the current guidelines all (near)-term neonates who meet the criteria for perinatal asphyxia and are classified as moderate or severe HIE by the Thompson score should receive this treatment.

During the hypothermic period the neonate may need a variety of different drugs ranging from anticonvulsants to sedatives or antibiotics. Simultaneously, different substances are being investigated for their additive neuroprotective effect. All these medications have a unique pharmacokinetic profile that could potentially be altered by the physical state of the neonate with HIE and hypothermia. The aim of this paper is to determine the effect that TH for neonates suffering from HIE has on the

pharmacokinetics of the drugs used during this hypothermic period, and whether dosing regimens need to be adjusted.

METHODS

A systematic search was performed on Pubmed, Embase and Cochrane library of all literature between 2000 and January 2020. A combination of the following search terms was used; therapeutic hypothermia, neonate, hypoxic ischemic encephalopathy and pharmacokinetics. In PubMed the corresponding MeSH terms for these search terms were used. An overview of the performed search results can be found in figure 1.

Only articles with full-text availability written in English were included. Another inclusion criterion was the reporting of a pharmacokinetic parameter for at least one of the following processes: absorption, distribution, metabolism or excretion. Only studies that concerned the human species were included. Reviews and study protocols that provided no new information, were excluded after screening references for secondary inclusion. Articles were excluded if the study population did not include term neonates or if therapeutic hypothermia was not applied.

First the titles of all articles were screened. If the relevance was unsure, the abstract was subsequently read. Finally, the resulting selected articles were thoroughly studied, and the references screened for secondary inclusion.

No Patient and Public Involvement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

RESULTS

A schematic overview of the entire data selection process can be found in figure 2. By using the above-mentioned search terms, a total of 380 publications were identified for screening, secondary inclusion included. The exact number of studies for each of the performed searches can be found in figure 1. After application of the inclusion and exclusion criteria and the removal of duplicates, the remaining 34 articles were deemed eligible for inclusion.

Characteristics of the selected articles can be found in table 1. Most of the studies were prospective multicentre observational studies. The drugs reviewed ranged from those that are the current standard treatment for the occurrence of neonatal seizures (i.e. phenobarbital), to various substances that have been hypothesised to have a neuroprotective effect in new-borns suffering from HIE. Some pharmacokinetic parameters were much more frequently analysed than others; total body clearance (C_L) was calculated in all but one of the articles, whereas absorption was only relevant in three analyses because most of the medication is administered intravenously. Only 8 out of 34 articles included a normothermic control group in the study design, which makes judging the effect of hypothermia on pharmacokinetics reliant on modelling such as Monte-Carlo simulations.

In an attempt to facilitate comparison of the pharmacokinetic parameters for absorption, distribution, metabolism and excretion described in the selected articles, the quantification of these parameters can be found in tables 2a-f. Because of the different characteristics of each drug administered during the hypothermic period, the included studies as presented in tables 2a-f were sorted by drug to facilitate the comparison. In the following data synthesis, first the effect of hypothermia on each of the pharmacokinetic parameters will be discussed. Next this will be applied to the different drugs that have been researched, to conclude with a dose recommendation for these medications.

Absorption

The rate and amount of absorption of a drug determines the maximum plasma concentration (C_{max}) and time needed to reach this peak concentration (t_{max}). Absorption can best be assessed by bioavailability, which can be calculated based on the area under the curve after oral (AUC_{PO}) versus intravenous (AUC_{IV}) administration, using the following formula: AUC_{PO}/AUC_{IV} x 100%. There are many factors that influence absorption after oral administration such as the speed of gastric emptying, food and physiochemical characteristics of the drug (dissolution, lipophilicity, etc). Pharmacokinetic factors in neonates can be different to those in adults, for example gastric emptying can be slower resulting in a longer t_{max} for drugs that are mainly absorbed in the duodenum [11].

However, absorption parameters are somewhat irrelevant in the context of TH as all drugs except for topiramate and melatonin are administered intravenously, where a bioavailability of 100% can be assumed. Topiramate has been hypothesised to improve the neuroprotective effect of therapeutic hypothermia[12].

Topiramate

Topiramate has a high oral bioavailability (±80%) in adults[13]. As topiramate is usually not used in children younger than 2 years, there are no available data on oral bioavailability in neonates. In all three articles the first dose of topiramate was 5 mg/kg and was administered via nasogastric tube. The two more recent studies went on to decrease the dose to 3 mg/kg for days 2-5, whereas Filippi et al. 2009[12] continued with 5 mg/kg for 3 days (table 2a). Both dosing regimens resulted in a steady state within the therapeutic range of 5-20 mg/L but reached steady state only after 48 hours. Filippi et al. 2009[12] made a distinction between mild hypothermia (33-34˚C) and deep hypothermia (30-33˚C) to assess if the depth of hypothermia has an impact on pharmacokinetics. Although no significant differences were found between the observed plasma concentrations and the calculated parameters, a lower AUC_{0-24} and steady state plasma concentration (C_{avg}), and a longer elimination half-life were observed in the deep hypothermia group. Due to the small sample size the differences were not

statistically significant, however, it is possible that these effects would become statistically significant in a larger study population. Nuñez-Ramiro et al. 2019[14] and Marques et al. 2019[15] both used the same dosing strategy, but only the first research group calculated the AUC_{0-24}, which was considerably lower than the one calculated by Filippi[12] (see table 2). Both groups concluded that a 5 mg/kg loading dose (LD) and 3 mg/kg as a maintenance dose (MD) was too low and the time needed to reach therapeutic concentrations too long. Since there is a significant correlation between serum level and seizure control it is desirable to reach steady state more quickly. The pharmacokinetic modelling suggests that a LD of 15 mg/kg followed by a MD of 5 mg/kg would lead to 90% of patients reaching therapeutic concentrations after 24 hours. Though the AUC was calculated in 2/3 studies, which is dependent on absorption as well as distribution, metabolism and elimination, unfortunately none of the studies mention quantifying bioavailability.

Melatonin

The hormone melatonin which regulates circadian rhythm, is produced by the pineal gland. In several animal models of HIE it has been shown to augment the neuroprotective efficacy of hypothermia by inhibiting apoptosis, stimulating anti-oxidant enzymes and by modulating the inflammatory response [16–18]. Balduini et al. 2019[19] are the first to have conducted a study with melatonin in humans, with only 5 infants included, in order to study the pharmacokinetics (table 2a). The authors administered melatonin by continuous drip over naso-/orogastric tube at 0.5 mg/kg over 4 hours, after which the absorption time was estimated to be 2.8 hours. Larger clinical studies to evaluate the efficacy of melatonin in neonates with HIE are therefore needed.

Distribution

Distribution is typically expressed as volume of distribution (V_D) which represents a virtual space that the drug has been dissolved in. V_D not only depends on substance characteristics but also several different patient factors which can differ between neonates and adults. For example babies have a

higher body water content which can imply that the V_D per kg is higher for water-soluble compounds such as paracetamol[20].

Out of the 34 articles included in this analysis, 28 calculated the V_D in some way, either central (V_c) or peripheral (V_P) or both (V_D). Only 2, however, actively describe a significant impact of the TH on distribution. Interestingly, Frymoyer et al. 2017 describe a 37% decrease in the V_D of morphine (8.0 L in TH versus 12.7 L for normothermia for an infant with mean birth weight of 3.5 kg), whereas Cies et al. 2017 on the other hand found a 30% increase of V_D for Ampicillin[21,22]. Both studies compared their own data to that of other previous studies, instead of a normothermic control group though[23,24].

Clearance: metabolization and excretion

After absorption and distribution, drugs are slowly cleared from the body by one of three ways; (1) they are excreted unchanged by the kidneys into the urine, (2) they are eliminated via other excretion routes such as bile, sweat, saliva or milk glands, and/or (3) they are metabolized mainly by the liver into a metabolite that can be both an inactive substance or a more active molecule compared to the original drug. Quantitatively, the largest group of metabolizing enzymes is the cytochrome-P450-mono-oxygenase family (CYP450). Tortorici et al. 2007[25] established that hypothermia impacted hepatic drug elimination by decreasing the activity of the CYP450 system, based on studies in brain-injured adults and healthy volunteers.

The sum of excretion in the urine of both the intact substance and metabolites that have been produced by the liver, further metabolization and excretion into bile, sweat, saliva or milk, make up the total body clearance (C_L). If for example a substance is primarily cleared by excretion in the urine, renal function is the principal determinate of the clearance. The Cochrane systematic review on TH could not observe any significant differences in urine output in neonates who underwent hypothermia compared to those who did not. Furthermore, meta-analysis showed that TH did not cause a significant

difference in the occurrence of renal impairment[2]. In the first week after birth there is maturation in renal function, the rate of which depends on the gestational age at birth, with premature neonates having a slower maturation than term neonates[26]. Creatinine is a degradation product of creatinine-phosphate which is produced by the muscles at a near constant speed and then filtered passively by the kidneys into the urine. Consequently, under normal circumstances it is a good biomarker for renal clearance, however studies show that even though you would expect serum creatinine to be low at birth because of low muscle mass, it actually peaks in the first 48 hours of life although there is no renal impairment. Therefore, serum creatinine might not be a good indicator of renal clearance for neonates in the first days after birth[27,28].

In total, 11 out of 34 studies demonstrated a significant decrease in total clearance as high as 46% during the hypothermic period (cfr tables 2a-2f).

Phenobarbital

Neonatal seizures in the context of HIE are treated in first-line with phenobarbital, an anti-epileptic drug that in adults has been replaced by other anti-epileptic agents with fewer adverse effects. Phenobarbital is metabolized in the liver mostly by CYP2C9 to inactive metabolites, which are then renally excreted together with 25% of unchanged phenobarbital[29]. None of the included studies measured the serum levels of phenobarbital metabolites so no conclusions can be drawn about the metabolism. About 66% of neonates with HIE and seizures respond to phenobarbital[30,31]. Pokorná et al. 2019[32] observed a slightly increased distribution and decreased clearance during hypothermia, although these changes were not statistically significant (table 2b). Similarly, none of the other included studies were able to detect a substantial effect of hypothermia on the pharmacokinetic parameters measured[30,31,33–35]. The therapeutic window for phenobarbital is 20-40 mg/L, which can be attained with a LD of 20 mg/kg that can be increased up to a maximum of 40 mg/kg if seizure control is not accomplished[31,34]. However a more recent study suggests to start at a higher dose of 30 mg/kg[30]. Some of the authors also continued with a MD ranging from 1.5 mg/kg to 8 mg/kg after

the LD depending on the study[32,34]. Other factors that were investigated for an effect on pharmacokinetic parameters were the severity of HIE and the influence of other medication. The severity was found to have an effect on phenobarbital clearance, likely because of a decreased cardiac output which leads to less blood flow to the kidneys and liver and a reduction in metabolic capacity[32]. Furthermore the concomitant administration of dobutamine also had an effect on phenobarbital clearance (although the authors suspect this was an artefact of the small sample size[35]).

Midazolam

A model compound of a drug metabolised by a CYP450 enzyme is midazolam, converted by CYP3A4 to 1-hydroxymidazolam (OHM) and successively to 1-hydroxymidazolam-glucuronide (HMG), both of which are sedative and further excreted renally. Midazolam is used as an add-on anti-epileptic agent when seizure control with phenobarbital monotherapy is inadequate (66% first line response) and provides an additional 23% of patients with seizure control. Intriguingly, none of the studies on midazolam showed an effect of hypothermia on the clearance of midazolam itself, although Favié et al. 2019 did find a significant reduction of the clearance of HMG (8.6%/˚C)[30,36,37] (table 2c). Midazolam is usually concomitantly used with phenobarbital, which is an inducer of CYP3A4. This means that the metabolization of midazolam is increased by 2.33-fold during co-medication with phenobarbital, as demonstrated by Favié et al. 2019. Thus, if another anti-epileptic drug is used as a first-line agent instead of phenobarbital, the dose of midazolam should be reduced by about 50%[30]. A point of attention is the occurrence of hypotension during treatment with midazolam as blood pressure and plasma concentrations of midazolam have a direct relationship, with blood pressure dropping by 3.6 mmHg for every increase in plasma concentration of 0.1 mg/L[37].

Lidocaine

If there is still no seizure control after adding midazolam, lidocaine can be added on as a third-line treatment, which is effective in 91% of the patients where seizure control could not be achieved with phenobarbital and midazolam alone. Lidocaine is a drug frequently used as a local anaesthetic or anti-

arrhythmic agent and is predominantly metabolised by CYP3A4 into the active monoethylglycinexylidide (MEGX) and subsequently glycine xylidide (GX), which is an inactive metabolite. The clearance of lidocaine was shown to be decreased by 24% (or 8,0%/˚C) during TH[38].

Morphine

Morphine is metabolised in the liver into two metabolites by the enzyme UDP-glucoronosyltransferase 2B7 (UGT2B7): morphine-3-glucoronide (M3G) and morphine-6-glucuronide (M6G). Both morphine and its less abundant metabolite M6G are analgesic and sedative, whereas M3G is inactive. Róka et al 2008[39] suspected the clearance of morphine and its metabolites to be decreased during therapeutic hypothermia (table 2d). They observed the median plasma concentration of morphine to be 292 ng/mL (137–767 ng/mL) during hypothermia, but only 206 ng/mL (88–327 ng/mL) in normothermic neonates (P = 0.014) even though the normothermic new-borns on average had received a higher dose of morphine. Unfortunately, the authors were unable to calculate the clearance of morphine in the hypothermic group because a steady state was not reached. It is therefore not possible to compare the results with those of the other studies. It did however raise the question of an altered clearance under hypothermia and inspired others to calculate what the authors had been unable to do. Frymoyer et al 2017[21] compared the pharmacokinetic parameters they observed in their prospective study during hypothermia to the data provided by Knibbe et al 2009[23] during normothermia. They concluded that V_D was decreased by 37.0% (or 12.3%/˚C) and the clearance of morphine by 46.7% (15.6%/˚C) in the new-borns treated with hypothermia. An interesting finding in this study was that the accumulation of M6G is dependent on the serum creatinine. Monte-Carlo simulations suggested that a LD of 50 µg/kg followed by a MD of 5 µg/kg or intermittent dosing of 40-50 µg/kg every 6 hours is recommended to stay within the therapeutic window. The results of these simulations were seconded by the findings of two open label prospective studies conducted in the Netherlands that have been reported by Favié et al 2019[40]. They found a decreased morphine clearance of 20.7% (or 6.98%/˚C) and of metabolites M3G and M6G of 14.7% (or 4.91%/˚C). They also concluded that during

the first five days of life there is a maturation of the enzyme UGT2B7 which results in an increase of morphine metabolization in this time.

Antibiotics

Gentamicin is an aminoglycoside antibiotic administered empirically to most neonates with HIE and is predominantly eliminated renally. Ideally the dose should generate a peak concentration of 10-12 mg/L and a trough concentration not exceeding 2 mg/L as this could cause oto- and nephrotoxicity. Liu et al. 2009[41] were the first to study the effect of TH on gentamicin pharmacokinetics (table 2e). They compared trough concentrations between normothermic and hypothermic group, which were not significantly different, but were, with a dose of 4-5 mg/kg every 24h, above 2 mg/L in 36-44% of neonates. They did however not calculate or measure other pharmacokinetic parameters but set the scene for better pharmacokinetic studies. Two retrospective studies observed a decrease by 25.0-35.3% (or 8.3-11.7%/˚C) in the C_L in neonates undergoing therapeutic hypothermia, and a significant increase in $t_{1/2}$[42,43]. Another study found an increase of 29% in clearance at post-natal age day 5, which can be considered as steady state normothermia after rewarming[44].

With regards to the dosing of gentamicin, many different schemes have been tried with an increasing interval between doses, ranging from 2.5 mg/kg every 12h[42] to 4 mg/kg every 24h[43] to 4-5mg/kg every 36h[43–46]. Just increasing the dosing interval from 24h to 36h brought the number of new-borns with trough concentrations under 2 mg/L from 62% to 96% without compromising on the percentage reaching the peak concentration[46]. But whatever dosing regimen is used, all studies recommend therapeutic drug monitoring (TDM) from the third dose onwards.

Apart from gentamicin, other antibiotics have also been investigated: ampicillin, amoxicillin, amikacin and benzylpenicillin. The Pharmacool study group observed a 55-56% increase in clearance of amoxicillin and benzylpenicillin after postnatal age day 5, which can be considered as reaching normothermic steady state[47,48]. After executing several simulations, the authors suggest implementing a gestational age (GA) dependant dosing regimen, with a lower dose for GA of 36-37

weeks. Both Cies et al. 2017[22] and Cristea et al. 2017[49] also calculated the clearance to be decreased (by 69.3% and 40.6% respectively) during TH, leading to the latter reducing the dosing frequency to once every 42h instead of every 30h. The percentage of neonates reaching toxic trough concentrations is thereby reduced from 40-76% to 14-17%[49]. They first compared their data to a previously published study to estimate this decrease in clearance[22,24].

Erythropoietin and Darbepoetin

In addition to therapeutic hypothermia, certain drugs have also been investigated for their neuroprotective effect[50–52]. Erythropoietin (EPO), most well-known for its hematopoietic effect, is not only produced by the kidneys but also by brain cells (astrocytes, neurons, oligodendrocytes). EPO binds to the EPO-receptor which is expressed by these same cells as well as by microglial and endothelial cells. It is proposed to have an anti-inflammatory effect in addition to inhibition of cell death and promotion of angiogenesis and development of new neurons and oligodendrocytes[53–56]. Combining EPO with therapeutic hypothermia is therefore hypothesised to have an additive neuroprotective effect[52,57–60]. The synthetic darbepoetin mimics the effects of EPO, but has a longer half-life, which would make a longer dosing interval possible (table 2f). Only a very small amount (<5%) of EPO, and thus darbepoetin, is excreted unchanged by the kidneys[61]. The majority is degraded in the body, possibly by intracellular degradation, of which the exact mechanisms are for the main part unknown[62].

Wu et al. 2012[63] performed a phase I prospective study to determine the optimal dosing of EPO in humans by testing different doses ranging from 250 U to 2,500 U/kg per dose every 48 hours. This article shows that with an increase in dose the clearance decreased from 15.6 ± 6.3 to 7.7 ± 0.9 mL/kg/h. The dose of 1,000 IU/kg had the best AUC and C_{max} for the administered dose (similar to those of a study with rats)[64]. Frymoyer et al. 2017[65], who included both the phase I trial mentioned above and the subsequent phase II study, found a C_L of 8.3 mL/kg/h which is considerably lower than a study reported for premature extremely low birth weight neonates (13.1 mL/kg/h)[66]. They also

concluded that neonates with HIE receiving TH will typically have a 50% higher exposure after the same EPO dose. The recommended dose used was 1,000 IU/kg every 24h for 3 doses and then 2 doses every 48h. The phase II trial found a clinical benefit of administering the EPO with significantly better brain MRI and motor function at 12 months[57]. The corresponding Phase III is momentarily still in progress.

Baserga et al. 2015[67] administered 2 doses of the EPO-derived molecule Darbe® (darbepoetin), one on day 0 and one on day 7. They divided the neonates into two treatment groups with one group receiving 2 µg/kg while the other was administered a higher dose of 10 µg/kg. A third placebo control group was needed to determine the baseline EPO as the quantification machines cannot distinguish between endogenously produced EPO and the synthetic Darbe®. The group receiving the higher dose had an AUC that best matched that of animal studies[64]. Roberts et al. 2015[68] also concluded that gestational age is inversely correlated with C_L, meaning that pre-term neonates have a higher clearance than term neonates.

DISCUSSION

It is difficult to compare pharmacokinetic data in HIE newborns with or without TH due to the small number of studies that include normothermic HIE controls, as TH is now standard practice in most countries. It would thus be unethical not to offer the best care (i.e. TH). Therefore, the control group are often neonates that do not suffer from HIE, which in turn makes it difficult to disentangle the effect of HIE from TH.

Phenobarbital is a relatively old anti-epileptic drug, which in adults has been substituted by newer agents. However, it remains one of the most effective anticonvulsive agents for neonatal seizures. Pending the outcome of ongoing comparative studies on the use of phenobarbital or levetiracetam as first line anti-epileptic[69], it is possible that levetiracetam will replace phenobarbital in the near future. However, as phenobarbital has an inducing effect on the metabolism of midazolam (which is often co-administered), if phenobarbital were to be replaced by levetiracetam, the dosage of midazolam needs to be reduced if we aim for similar exposure [30].

This article only explored the impact of HIE+HT on the pharmacokinetics in neonates. But in reality, the pharmacodynamics, the effect that the drug has on the body, also needs to be considered. In anticonvulsants this means the seizure control response as seen on amplitude integrated EEG. The only study in which this was quantified, is Van den Broek et al. 2012[31] who found that administering phenobarbital to neonates undergoing hypothermia reduced transition from continuous normal voltage to discontinuous normal voltage aEEG background level. The only other pharmacodynamic parameter evaluated is target attainment of antibiotics which was calculated using the $fT > MIC$ ratio, which is the time that the free concentration of the substance is higher than the minimal inhibitory concentration. Although Cies et al. 2017[22] administered 100 mg/kg ampicillin every 8 hours, their modelling predicted that 25 or 50 mg/kg every 24 hours would actually be sufficient to attain a target

of 50% and even 100% of time above MIC. Bijleveld et al. 2018[48] also used simulations to recommend a gestational age (GA) dependent dosing regimen; 50mg/kg/d of amoxicillin for GA of 36-37w and 75mg/kg/d for GA 38-42 in three doses for 7 days, which result in target attainment of 100% for *Streptococcus agalactiae* and *Listeria monocytogenes*. The Dutch paediatric formulary currently advises a dose of 75 mg/kg/d in three doses for all neonates that are younger than 7 days postnatal age and have birth weight of over 2 kg [74].

After reviewing the literature above, the following dosage recommendations can be suggested (table 3). The Dutch paediatric formulary is slowly being updated to include specific dosing regimens for this specific setting [75]. As can be seen in table 3, some of the less frequently used agents still need to be added, commonly because additional validation is still needed. Therapeutic drug monitoring can be used to verify if the following drugs are within the therapeutic range: phenobarbital, midazolam, topiramate, and gentamicin.

CONCLUSION

The aim of this paper was to determine the effect of lowering the core body temperature of the neonate with HIE, on the pharmacokinetics of different drugs used during this hypothermic period. This was evaluated by comparing values for the different pharmacokinetic processes; absorption, distribution, metabolisation and elimination. Depending on the drug, hypothermia can have an effect on certain parameters of its pharmacokinetics. Dosage recommendations, based on these changes as observed in the reviewed literature, were compared to those published by the Dutch paediatric formulary.

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This paper is an adapted version of the master thesis written by I. Lutz. None of the authors have competing interests to declare, and there was no funding to write this paper.

LISTS OF TABLE AND FIGURE LEGENDS

Table 1: Study Characteristics

Table 2a-f: Overview of all selected articles.

Table 3: Recommended dosing of medication used in newborns with hypoxic ischemic encephalopathy. Loading dose = LD, Maintenance dose = MD based on the Dutch paediatric formulary [75].

Figure 1: Flow chart on search strategy, search terms and number of hits in PubMed, Embase and Cochrane.

Figure 2: Flow diagram of data selection and subsequent results.

AUTHOR'S CONTRIBUTIONS

Isabelle Claire Lutz, MD

was responsible for the study design, conducted the literature search and was responsible for the writing process of the manuscript. She finalized the final version, and approved the final draft.

Karel Allegaert, MD, PhD

assisted in the writing process of the paper, supervised the final version and approved the final draft. He is the corresponding author to the paper.

Jan de Hoon, MD, PhD

was responsibility for the study design, assisted in the writing process of the paper and approved the final draft.

Heleen Marynissen, MD, PhD student

was responsible for the study design, assisted in the literature search and the writing process of the paper, supervised the final version and approved the final draft.

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TABLES

Table 1: Study Characteristics

Characteristic	No.
Type of study	**34**
Prospective observational	27
Retrospective observational	6
Mixed	1
Medication	**34**
Anticonvulsant	10
Phenobarbital	6
Midazolam	3
Lidocaïne	1
Antibiotics	11
Gentamicin	8
Ampicillin	1
Amoxicillin	1
Benzyl Penicillin	1
Analgesic/sedative	3
Morphine	3
Various neuroprotective	10
Erythropoietin	2
Darbepoietin	2
Topiramate	3
Bumetanide	2
Melatonin	1
Pharmacokinetic parameter	
Absorption	3
Distribution (V_D)	28
Metabolic clearance	5
Excretion (C_L)	33
Elimination half-life	17
Normothermic controls	
Yes	8
No	26

Table 2a-f: Overview of all selected articles.

VD = volume of distribution, CL = total body clearance, t1/2 = half-life, NT = normothermia, TH = therapeutic hypothermia, DH = deep hypothermia, MH = moderate hypothermia, PNA = postnatal age, OHM = 1-hydroxymidazolam, HMG = 1-hydroxymidazolam-glucuronide, MEGX = monoethylglycinexylidide, M3G = morphine-3-glucoronide, M6G = morphine-6-glucuronide

Table 2a: *topiramate and melatonin*

Topiramaat	n =	Study type	Absorption	V_D (L/kg)	Metabolite C_L (mL/kg/h)	C_L (mL/kg/h)	$t_{1/2}$ (h)
Filippi et al. 2009[12]	13	Prospective	AUC = 343,2 mg/L/h	/	/	MH = 13,87 DH = 15,72	MH = 29 DH = 49
Nuñez-Rqmiro et al. 2019[14]	106	Prospective (RCT)	AUC = 77,8 mg/L/h	/	/	19,7	54,1
Marques et al. 2019[15]	52	Prospective (RCT)	/	0,976	/	TH = 12,6 Post-warm = 15,3 **↓ 20,8% = ↓ 6,95%/˚C**	/
Melatonin							
Balduini et al. 2019[19] **(Melatonine)**	5	Prospective	AUC_{ss} = 9,71 µg/mL/h t_{abs} = 2,8h	1,8	/	46,0	26,4

Table 2b*: phenobarbital*

Phenobarbital	n =	Study type	Absorption	V_D (L/kg)	Metabolite C_L (mL/kg/h)	C_L (mL/kg/h)	$t_{1/2}$ (h)
Van den broek et al. 2012[31]	31	Prospective	/	0,986	/	4,914	140
Shellhaas et al 2013[33]	39	Retrospective	/	0,92	/	7,6	85
Filippi et al 2011[34]	19	Prospective	/	1,56	/	6,38	173,3
Favié et al 2019[30]	113	Prospective	/	1,03	/	2943 (?)	/
Pokorná et al 2019[32]	40	Prospective	/	0,519	/	2,1	120
Síma et al 2015[35]	37	Prospective	/	0,48	/	3,4	93,7

Table 2c*: midazolam and lidocaine*

Midazolam	n =	Study type	Absorption	V_D (L/kg)	Metabolite C_L (mL/kg/h)	C_L (mL/kg/h)	$t_{1/2}$ (h)
Welzing et al. 2013[36]	9	Prospective	/	5,91 L (median weight not	/	154,0	7,0

				calculated)			
Van den Broek et al 2015[37]	53	Prospective	/	1,93	OHM = 0,7 HMG 0,02	268,0	5,0
Favié et al. 2019[30]	118	Prospective	/	1,55	OHM = 0,969 **↓25,7% = ↓8,6%/˚C** HMG = 0,055	100	/
Lidocaïne							
Van den Broek et al. 2013[38]	48	Mixed	/	3,11	MEGX = 0,166	397,0 **↓24,0% = ↓8,0%/˚C**	5,5

Table 2d: *morphine*

Morphine	**n =**	**Study type**	**Absorption**	**V_D (L/kg)**	**Metabolite C_L (mL/kg/h)**	**C_L (mL/kg/h)**	**$t_{1/2}$ (h)**
Favié et al 2019[40]	244	Prospective	/	2,54	M3G = 0,130 M6G = 0,494 **↓14,7% = ↓4,91%/˚C**	259,0 **↓20,7% = ↓6,89%/˚C**	/
Róka et al 2018[39]	16	Observational	/	/	/	'could not be calculated'	/
Frymoyer et al 2016[21]	20	Prospective	/	2,286 **↓37,0% = ↓12,3%/˚C**	M3G = 0,188 M6G = 0,197	216,0 **↓46,7% = ↓15,6%/˚C**	/

Table 2e*: antibiotics*

Gentamicin	**n =**	**Study type**	**Absorption**	**V_D (L/kg)**	**Metabolite C_L (mL/kg/h)**	**C_L (mL/kg/h)**	**$t_{1/2}$ (h)**
Bijleveld et al. 2016[44]	47	Prospective	/	0,897	/	60 (day 2) 77,4 (29%↑ day 5)	/
Liu et al. 2009[41]	55	Prospective	/	/	/	/	/
Frymoyer et al. 2013[45]	29	Retrospective	/	0,47	/	36,0	/
Ting et al. 2014[42]	46	Retrospective	/	NT = 0,45 HT = 0,41	/	NT = 51,0 HT = 33,0 **↓35,3% = ↓11,7%/˚C**	NT = 7,0 HT = 9,6
Mark et al. 2013[43]	23	Retrospective	/	/	/	NT = 50,0 HT = 40,0 **↓25% = ↓8,3%/˚C**	NT = 6,6 HT = 9,2 **40%↑**
Frymoyer et al. 2013[46]	52	Retrospective	/	/	/	17,0	/
Cies et al. 2018[70]	12	Prospective	/	0,87	/	132,0	/
Martinkova et al. 2010[71]	35	Prospective	/	0,40	/	46,0	/
Other antibiotics							
Cies et al. 2017 (Ampicilline)[22]	13	Prospective	/	0,52	/	25,8	/
Bijleveld et al. 2018 (Amoxicillin)[48]	125	Prospective	/	0,34 (V_C)	/	PNA 0-4 = 90,0 PNA 5 = 140,0 **55%↑**	/
Bijleveld et al. 2018[47]	41	Prospective	/	0,62 (V_C)	/	PNA 0-4 = 160,0	/

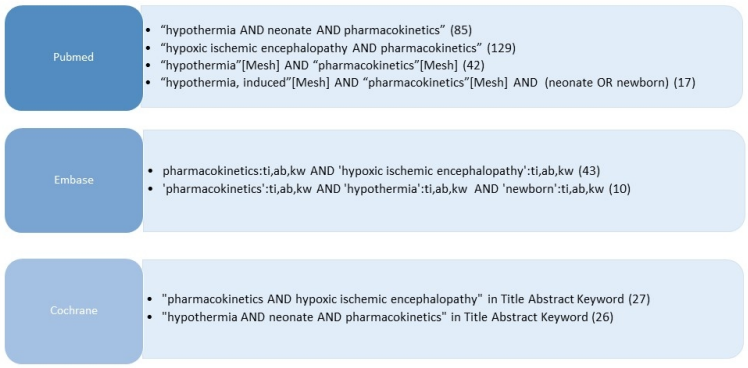
(Benzylpenicillin)						PNA 5 = 250,0 **56%↑**	
Cristea et al. 2017 (Amikacin)[49]	56	Retrospective	/	0,832	/	49,5 **↓40,6% = ↓13,5%/°C**	/

***Table 2f**: erythropoietin, darbepoietin, bumetanide*

Erythropoietin	n =	Study type	Absorption	V_D (L/kg)	Metabolite C_L (mL/kg/h)	C_L (mL/kg/h)	$t_{1/2}$ (h)
Frymoyer et al. 2017[65]	47	Prospective	/	V_C = 0,074 V_P = 0,096	/	8,3	/
Wu et al. 2012[63]	24	Prospective	/	0,095-0,178	/	7,7-15,6 C_L↓ with dose↑	/
Roberts et al. 2015[68]	26	Prospective	/	0,511	/	15,0	23,6
Baserga et al. 2015[67]	30	Prospective	/	/	/	40,0-50,0	24-35
Miscellaneous							
Julien et al. 2016[72] **(Bumetanide)**	14	Prospective	/	0,23	/	19,8	8.4
Pressler et al. 2015[73] **(Bumetanide)**	14	Prospective	/	0,23	/	19,8	8.4

Table 3: Recommended dosing of medication used in newborns with hypoxic ischemic encephalopathy. Loading dose = LD, Maintenance dose = MD based on the Dutch paediatric formulary [75].

	Loading dose	Frequency	Maintenance dose	www.kinderformularium.nl	Hypothermic situation specific
Phenobarbital	20 – 40 mg/kg	Bolus	/	LD = 20 – 40 mg/kg, MD = 2,5 – 5 mg/kg in 2 doses/day	Yes
Morphine	50 µg/kg	Continuous	5 µg/kg/h	LD = 25 – 50 µg/kg, MD = 3 – 20 µg/kg/h	No
Midazolam	0,05-0,1 mg/kg	Continuous	0,05 – 0,1 mg/kg/h	LD = 0,05 mg/kg, MD 0,05 – 0,1 mg/kg/h	Yes
Lidocaine	>2,0-2,5kg: 2 mg/kg (10 min) <2,5-4,5kg: 2 mg/kg (10 min)	Continuous: MD 3,5h -> ½ MD 12h -> ¼ MD 12h	6 mg/kg/h 7 mg/kg/h	LD 2 mg/kg (10 min) -> 4 mg/kg/h (6h) -> 2 mg/kg/h (12h) -> stop	Yes
Topiramate	15 mg/kg		5 mg/kg/d	No dose for this indication mentioned	
Erythropoietin	/	24h (3x) then 48h (2x)	1.000 U/kg	No dose for this indication mentioned	
Darbepoetin	/	7d (2x)	10 mcg/kg	No dose for this indication mentioned	
Gentamicin	/	36 h (5x)	4-5 mg/kg	5 mg/kg every 36h	Yes



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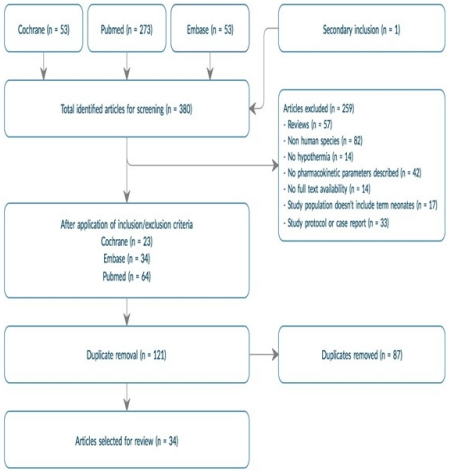

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Pharmacokinetics during therapeutic hypothermia for neonatal hypoxic ischemic encephalopathy: a literature review

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ABSTRACT

Background Neonatal hypoxic ischemic encephalopathy due to perinatal asphyxia, can result in severe neurodevelopmental disability or mortality. Hypothermia is at present the only proven neuroprotective intervention. During hypothermia, the neonate may need a variety of drugs with their specific pharmacokinetic profile. The aim of this paper is to determine the effect that hypothermia for neonates suffering from hypoxic ischemic encephalopathy has on the pharmacokinetics and to what extent dosing regimens need adjustments.

Method A systematic search was performed on Pubmed, Embase and Cochrane library of literature (2000-2020) using a combination of the following search terms; therapeutic hypothermia, neonate, hypoxic ischemic encephalopathy and pharmacokinetics. Titles and abstracts were screened, and inclusion/exclusion criteria were applied. Finally, relevant full-texts were read, and secondary inclusion was applied on the identified articles.

Results A total of 380 articles were retrieved, and 34 articles included after application of inclusion/exclusion criteria and duplicate removal, 2 additional papers were included as suggested by the reviewers. Twelve (12) out of 36 studies on 15 compounds demonstrated a significant decrease in clearance, be it that the extent differs between routes of elimination and compounds, most pronounced for renal elimination (phenobarbital no difference, midazolam metabolite -21%, lidocaine -24%; morphine -21 to -47%, gentamicin -25 to -35%, amikacin -40%) during hypothermia. The data as retrieved in literature were subsequent compared to the dosing regimen as stated in the Dutch paediatric formulary.

Conclusion Depending on the drug-specific disposition characteristics, therapeutic hypothermia in neonates with hypoxic ischemic encephalopathy affects pharmacokinetics.

What's known

Therapeutic hypothermia has a neuroprotective effect for neonates with hypoxic ischemic hypothermia.

Hypoxic ischemic asphyxia and lowering the core body temperature has impact on the pharmacokinetics, up to the level that dosing regimens for these neonates should be adapted.

What's new

Compared to the latest structured review (2015) on pharmacokinetics during hypothermia for 4 compounds (gentamicin, topiramate, phenobarbital, morphine), the current systematic search provides data on 15 compounds, reflecting the relevant progress made.

A significant decrease in clearance is observed in neonates during therapeutic hypothermia, be it that the extent differs between routes of elimination and compounds, but most pronounced for renal elimination (phenobarbital no difference, midazolam metabolite -21%, lidocaine -24%; morphine -21 to -47%, gentamicin -25 to -35%, amikacin -40%) during hypothermia.

INTRODUCTION

Neonatal hypoxic ischemic encephalopathy (HIE), brain damage sustained as a result of perinatal asphyxia, occurs in 1.5 out of 1000 births[1] and can result in severe neurodevelopmental disability or mortality in respectively 24.9% and 34.1% of cases[2]. Perinatal asphyxia is a condition characterised by a persistently low APGAR-score (≤5) assessed at 5 and 10 minutes after birth, or metabolic acidosis, defined as a pH of <7.0 and/or base deficit of ≥16 mmol/L, measured in the foetal umbilical artery or arterial blood within 1 hour after birth[3,4]. The HIE severity can be categorised by the Sarnat score into mild, moderate and severe brain injury based on the abnormality of level of consciousness, spontaneous activity, posture, tone, primitive reflexes and autonomic function[5]. Alternatively, the Thompson score is another scoring system that uses similar criteria like Sarnat but also includes the presence of seizures and fontanelle tension; Both scores can be used for prognosis and provide prognostic value and quantify HIE into mild, moderate and severe [6].

Therapeutic hypothermia (TH) is at present the only proven effective intervention for moderate and severe HIE. It significantly reduces the mortality by 8.8% and severe morbidity by 15.4% (relative risk = 0.75; number needed to treat = 7)[2]. In its current approach, TH aims to cool the body temperature of the neonate to 33.5˚C for the duration of 72 hours within 6 hours after birth, and a subsequently gradual rewarming at a rate of 0.3-0.5˚C per hour[7–10]. According to the current guidelines all (near)-term neonates who meet the criteria for perinatal asphyxia and are classified as moderate or severe HIE by the Thompson score should receive this treatment [5,6].

During the hypothermic period the neonate may need a variety of different drugs ranging from anti-epileptic drugs to sedatives or antibiotics. Simultaneously, different substances with different mechanisms involved are investigated on their additive neuroprotective effect. We refer the interested reader to a recent review on the pharmacodynamics of these claimed neuroprotective compounds[11]

However, for any drug administered to these patients, the pharmacokinetic profile may be altered by the physical state of the neonate with HIE and TH. This is due to the altered pathophysiology explained by both the disease (asphyxia) and the intervention (TH), and includes renal impairment, altered haemodynamics like cardiac output and blood flow, or altered hepatic function [Smits et al, Frontiers Pharmacol][12]. The aim of this paper is to provide an overview on the effects of TH in neonates suffering from HIE have on the pharmacokinetics of drugs administered during this hypothermic period, and whether dosing regimens need to be adjusted.

METHODS

A systematic search was performed on Pubmed, Embase and Cochrane library of all literature between 1 January 2000 and 1 January 2020. A combination of the following search terms was hereby used: "therapeutic hypothermia, neonate, hypoxic ischemic encephalopathy and pharmacokinetics". In PubMed the corresponding MeSH terms for these search terms were used. An overview of the performed search and the subsequent results is provided in Figure 1.

Only articles with full-text availability written in English were included. Another inclusion criterion was the reporting of a pharmacokinetic parameter for at least one of the following processes: absorption, distribution, metabolism or excretion. Only studies that concerned the human species were included. Reviews and study protocols that provided no new information, were excluded after screening references for secondary inclusion. Articles were excluded if the study population did not include term neonates or if TH was not applied.

First the titles of all articles were screened. If the relevance was unsure, the abstract was subsequently read. Finally, the resulting selected articles were thoroughly studied, and the references screened for secondary inclusion.

Patient and Public Involvement

This research was conducted without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

RESULTS

A schematic overview of the entire data selection process can be found in Figure 2. By using the above-mentioned search terms, a total of 380 publications were identified for screening, secondary inclusion included. The exact number of studies for each of the performed searches can be found in Figure 1. After application of the inclusion and exclusion criteria and removal of duplicates, the remaining 34 articles were deemed eligible for inclusion. To keep the overview updated, two additional papers (2-iminobiotin, lidocaine) that were not in the initial search strategy, but were suggested by the reviewers were added in the revised version of the paper (both very recent publications, not in the initial search).

Characteristics of all retained (n=36)articles are provided in Table 1. Most of the studies were prospective multicentre observational studies. The drugs reviewed ranged from those that are the current standard treatment for the occurrence of neonatal seizures (i.e. phenobarbital), to various substances that have been hypothesised to have a neuroprotective effect in newborns suffering from HIE. Some pharmacokinetic parameters were much more frequently analysed than others. Total body clearance (C_L) was calculated in all but one of the articles, whereas absorption was only relevant in three analyses as most of the drugs are administered by intravenous route. Only 10 out of 36 articles included a normothermic control group in the study design. More common, the quantification of the effect of TH on pharmacokinetics was based on data pooling or literature data, and subsequent use of population pharmacokinetic modelling approaches.

In an attempt to facilitate comparison of the pharmacokinetic parameters for absorption, distribution, metabolism and excretion described in the selected articles, the quantification of these parameters can be found in Tables 2a-f. Because of the different characteristics of each drug administered during

the hypothermic period, the included studies as presented in Tables 2a-f were sorted by drug to facilitate comparison. In the subsequent synthesis, the effect of TH on each of the pharmacokinetic parameters will be discussed, illustrated by available findings for different drugs.

Absorption

The rate and amount of absorption of a drug determines the maximum plasma concentration (C_{max}) and time needed to reach this peak concentration (t_{max}). Absorption can best be assessed by bioavailability, which can be calculated based on the area under the curve after oral (AUC_{PO}) versus intravenous (AUC_{IV}) administration, using the following formula: AUC_{PO}/AUC_{IV} x 100%. There are many factors that influence absorption after oral administration such as gastric emptying, food and physico-chemical characteristics of the drug. These factors can be different in neonates when compared to adults, so that for example differences in gastric emptying rate will affect the t_{max} for drugs that are mainly absorbed in the duodenum [13]. However, absorption parameters are less relevant in the context of TH as all drugs except for topiramate and melatonin are administered intravenously, where a bioavailability of 100% can be assumed.

Topiramate

Topiramate has been hypothesised to improve the neuroprotective effect of TH, with glutamate-receptor inhibition as underlying claimed mechanism [14]. In adults, it has a high oral bioavailability (±80%)[15]. As topiramate is usually not used in children younger than 2 years, there were no available pharmacokinetic data on in neonates. In all three articles, the first dose of topiramate was 5 mg/kg and was administered via nasogastric tube. The two more recent studies went on to decrease the dose to 3 mg/kg for days 2-5, whereas Filippi et al. 2009[14] continued with 5 mg/kg for 3 days (Table 2a). Both dosing regimens resulted in a steady state within the therapeutic range of 5-20 mg/L but steady state was only reached after 48 hours. Filippi et al. 2009[14] made a distinction between mild hypothermia (33-34˚C) and deep hypothermia (30-33˚C) to assess if the depth of hypothermia had an

impact on pharmacokinetics. Although no significant differences were found between the observed plasma concentrations and the calculated parameters, a lower AUC_{0-24} and steady state plasma concentration (C_{avg}), and a longer elimination half-life were observed in the deep hypothermia group. Due to the small sample size the differences were not statistically significant, however, it is possible that these effects would become statistically significant in a larger study population. Nuñez-Ramiro et al. 2019[16] and Marques et al. 2019[17] both used the same dosing strategy, but only the first research group calculated the AUC_{0-24}, which was considerably lower than the one calculated by Filippi[14] (see Table 2a). Both groups concluded that a 5 mg/kg loading dose (LD) and 3 mg/kg as a maintenance dose (MD) was too low and the time needed to reach therapeutic concentrations too long. Since there is a strong correlation between serum level and seizure control or neuroprotective effects, it is desirable to reach steady state more quickly. The pharmacokinetic modelling suggests that a LD of 15 mg/kg followed by a MD of 5 mg/kg would lead to 90% of patients reaching therapeutic concentrations after 24 hours. Though the AUC was calculated in 2/3 studies, this parameter does not only depend on absorption, but is also affected by subsequent distribution, metabolism and elimination. Unfortunately, in the absence of intravenous PK data in neonates, quantification of bioavailability and the impact of asphyxia and TH a cannot be assessed.

Melatonin

The hormone melatonin which regulates circadian rhythm, is produced by the pineal gland. In several animal models of HIE it has been shown to augment the neuroprotective efficacy of hypothermia by inhibiting apoptosis, stimulating anti-oxidant enzymes and by modulating the inflammatory response [18–20]. Balduini et al. 2019[21] are the first to have conducted a study with melatonin in humans, with only 5 infants included, in order to study the pharmacokinetics (Table 2a). The authors administered melatonin by continuous drip over naso-/orogastric tube at 0.5 mg/kg over 4 hours, after which the absorption time was estimated to be 2.8 hours. Larger clinical studies to evaluate the efficacy of melatonin in neonates with HIE are therefore needed.

Distribution

Distribution is typically expressed as volume of distribution (V_D) which represents a virtual space that the drug has been dissolved in. V_D not only depends on substance characteristics but also patient factors which can be different between neonates and adults. For example, neonates have a proportional higher body water content which can imply that the V_D per kg is higher for water-soluble compounds[22].

Out of the 36 articles included in this analysis, 30 reported on aspects of the V_D, sometimes based on a central (V_c) and peripheral (V_P) distribution volume. However, only 2/30 articles described a significant impact of the TH on distribution. Interestingly, Frymoyer et al. 2017 describe a 37% decrease in the V_D of morphine (8.0 L in TH versus 12.7 L for normothermia for an infant with mean birth weight of 3.5 kg), whereas Cies et al. 2017 on the other hand found a 30% increase of V_D for Ampicillin[23,24]. Both studies compared their own data to earlier reported studies in literature, instead of a dataset of normothermic controls integrated in the same analysis [25,26].

Clearance: metabolization and excretion

After absorption and distribution, drugs are slowly cleared from the body by one of three ways; (1) excretion, unchanged by the kidneys, (2) elimination via other excretion routes such as bile, sweat, saliva or milk glands, and/or (3) metabolization mainly by the liver into metabolite(s) that can be both an inactive substance or a more active molecule compared to the mother compound. Such metabolites commonly subsequently undergo additional metabolism or are eliminated by renal or other excretion routes. Quantitatively, the largest group of metabolizing enzymes is the cytochrome-P450-mono-oxygenase family (CYP450). Tortorici et al. 2007[27] established that hypothermia impacted hepatic drug elimination by decreasing the activity of the CYP450 system, based on studies in brain-injured adults and healthy volunteers. However, such findings need to be intergrated with iso-enzyme specific ontogeny in neonates[12]. The sum of excretion in the urine of both the intact substance and

metabolites that have been produced by the liver, further metabolization and excretion into bile, sweat, saliva or milk, make up the total body clearance (C_L).

If for example a substance is primarily cleared by excretion in the urine, renal function is the principal determinate of clearance. The Cochrane systematic review on TH could not observe any significant differences in urine output in neonates who underwent TH compared to those who did not. Furthermore, meta-analysis showed that TH did not cause a significant difference in the occurrence of renal impairment[2]. This suggests that the asphyxia, and not the intervention is the major determinant of altered renal elimination clearance. In the first week after birth there is maturation in renal function, the rate of which depends on the gestational age at birth, with premature neonates displaying a slower maturation than term neonates[28]. Creatinine is a degradation product of creatine which is produced by the muscles at a near constant speed and subsequently filtered passively by the kidneys into the urine. Consequently, under normal circumstances it is a good biomarker for renal clearance, however studies show that birth creatinine reflects maternal creatinine values to subsequently peak in the first 48 hours of life irrespective from the presence of renal impairment related to asphyxia[29,30]. Therefore, serum creatinine might not be a good indicator of renal clearance for neonates in the first days after birth[31,32]. In total, 13 out of 36 studies demonstrated a significant decrease in total clearance as high as 46% during TH (Tables 2a-2f).

Phenobarbital

Neonatal seizures in the context of HIE are treated in first-line with phenobarbital, an anti-epileptic drug that in adults has been replaced by other anti-epileptic agents with fewer adverse effects. Phenobarbital is metabolized in the liver mostly by CYP2C9 to inactive metabolites, which are then renally excreted together with 25% of unchanged phenobarbital[33]. None of the included studies measured the serum levels of phenobarbital metabolites so no final conclusions can be drawn about metabolism. About 66% of neonates with HIE and seizures respond to phenobarbital[34,35]. Pokorná et al. 2019[36] observed decreased clearance during TH, although these changes were not statistically

significant (Table 2b). Similarly, none of the other included studies were able to detect a substantial effect of TH on the pharmacokinetic parameters measured[34,35,37–39]. The therapeutic window for phenobarbital is 20-40 mg/L, which can be attained with a LD of 20 mg/kg that can be increased up to a maximum of 40 mg/kg if seizure control is not attained[35,38]. However a more recent study suggests to start at a higher dose of 30 mg/kg[34]. Some of the authors also continued with a MD ranging from 1.5 mg/kg to 8 mg/kg after the LD depending on the study[36,38]. Other factors that were investigated for an effect on pharmacokinetic parameters were the severity of HIE and the influence of other drug. The severity was found to have an effect on phenobarbital clearance, likely because of a decreased cardiac output which leads to less blood flow to the kidneys and liver and a reduction in metabolic capacity. This suggest that disease severity is a more prominent covariate of phenobarbital clearance compared to TH[36]. Furthermore, concomitant dobutamine administration also had an effect on phenobarbital clearance (although the authors suspect this was an artefact of the small sample size[39]).

Midazolam

A model compound of a drug metabolised by a CYP450 enzyme is midazolam, converted by CYP3A4 to 1-hydroxymidazolam (OHM) and successively to 1-hydroxymidazolam-glucuronide (HMG), both of which are sedative and further excreted by renal route. Midazolam is used as an add-on anti-epileptic agent when seizure control with phenobarbital monotherapy is inadequate (see higher, 66% first line response) and provides an additional 23% of patients with seizure control. Intriguingly, none of the studies on midazolam showed an effect of TH on midazolam clearance. However, Favié et al. reported on a significant reduction of the clearance of HMG (8.6%/˚C), likely reflecting the impact of renal impairment [34,40,41] (Table 2c). Midazolam is usually concomitantly used with phenobarbital, which is an inducer of CYP3A4. This effect has been quantified, so that midazolam metabolic clearance is increased by 2.33-fold during co-medication with phenobarbital, as demonstrated by Favié et al. 2019. Thus, if another anti-epileptic drug is used as a first-line agent instead of phenobarbital, the dose of midazolam should be reduced by about 50%[34]. A point of attention is the occurrence of hypotension

during treatment with midazolam as blood pressure and plasma concentrations of midazolam have a direct relationship, with blood pressure dropping by 3.6 mmHg for every increase in plasma concentration of 0.1 mg/L[41].

Lidocaine

If there is still no seizure control after adding midazolam, lidocaine can be added as a third-line treatment, which is effective in 91% of the patients where seizure control could not be achieved with phenobarbital and midazolam alone. Lidocaine is a drug frequently used as a local anaesthetic or anti-arrhythmic agent and is predominantly metabolised by CYP3A4 into the active monoethylglycinexylidide (MEGX) and subsequently glycine xylidide (GX), which is an inactive metabolite. The clearance of lidocaine was shown to be decreased by 24% (or 8,0%/˚C) during TH[42]. The extent of the impact of TH on lidocaine pharmacokinetics has recently been confirmed (decrease 21%, 7.26%/°C) in a further extended cohort of patients, including 49 neonates undergoing TH (prospective validation)[43].

Morphine

Morphine is metabolised in the liver into two metabolites by the enzyme UDP-glucoronosyltransferase 2B7 (UGT2B7): morphine-3-glucoronide (M3G) and morphine-6-glucuronide (M6G). Both morphine and its less abundant metabolite M6G are analgesic and sedative, whereas M3G is inactive. Róka et al 2008[44] concluded that the clearance of morphine and its metabolites were decreased during TH (Table 2d). This conclusion was based on differences in median morphine plasma concentration [292 ng/mL (137–767 ng/mL) during TH to 206 ng/mL (88–327 ng/mL) in normothermic neonates (P = 0.014)] even though the normothermic newborns on average had received a higher dose of morphine. Unfortunately, the authors were unable to report on morphine pharmacokinetics. It is therefore not possible to compare the results with the subsequent studies. However, it did raise the question of altered clearance under TH and inspired others. Frymoyer et al 2017[23] compared the pharmacokinetic parameters observed in their prospective study during TH to the data provided by

Knibbe et al 2009[25] during normothermia. They concluded that morphine clearance was decreased by 46.7% (15.6%/˚C) in newborns treated with TH. An interesting finding in this study was that M6G accumulation is dependent on the serum creatinine. Monte-Carlo simulations suggested that a LD of 50 µg/kg followed by a MD of 5 µg/kg or intermittent dosing of 40-50 µg/kg every 6 hours is recommended to stay within the therapeutic window. The results of these simulations were seconded by the findings of two open label prospective studies conducted in the Netherlands reported by Favié et al 2019[45]. They found a decreased morphine clearance of 20.7% (or 6.98%/˚C) and of metabolites M3G and M6G of 14.7% (or 4.91%/˚C) during TH. The authors subsequently observed that over the subsequent first five days of life there is an increase in clearance, the phenotypic final result of maturation of UGT2B7 activity, disease recovery and finalization of TH.

Antibiotics

Gentamicin is an aminoglycoside antibiotic administered empirically to most neonates with HIE and is predominantly eliminated renally. Ideally the dose should generate a peak concentration of 10-12 mg/L and a trough concentration not exceeding 2 mg/L as this could cause oto- and nephrotoxicity. Liu et al. 2009[46] were the first to study the effect of TH on gentamicin pharmacokinetics (Table 2e). They compared trough concentrations between normothermic and hypothermic group, which were not significantly different, but were, with a dose of 4-5 mg/kg every 24h, above 2 mg/L in 36-44% of neonates. They did however not calculate or measure other pharmacokinetic parameters but set the scene for better pharmacokinetic studies. Two retrospective studies observed a decrease by 25.0-35.3% (or 8.3-11.7%/˚C) in the C_L in neonates undergoing TH, and a significant increase in $t_{1/2}$[47,48]. Another study found an increase of 29% in clearance on postnatal age day 5, which can be considered as steady state normothermia after rewarming[49].

With regards to gentamicin dosing, many different schemes have been explored with an increasing interval between doses, ranging from 2.5 mg/kg every 12h[47] to 4 mg/kg every 24h[48] to 4-5mg/kg every 36h[48–51]. Just increasing the dosing interval from 24h to 36h reduced the number of

newborns with trough concentrations under 2 mg/L from 62% to 96% without compromising on the percentage reaching the peak concentration[51]. But whatever dosing regimen is used, all studies recommend therapeutic drug monitoring (TDM), and the same holds true for other aminoglycosides (like amikacin)[49].

Apart from gentamicin, other antibiotics have also been investigated: ampicillin, amoxicillin, amikacin and benzylpenicillin. The Pharmacool study group observed a 55-56% increase in clearance of amoxicillin and benzylpenicillin after postnatal age day 5, which can be considered as reaching normothermic steady state[52,53]. Based on subsequent simulations, the authors suggest implementing a gestational age (GA) dependent dosing regimen, with a lower dose for GA of 36-37 weeks. Both Cies et al. 2017[24] and Cristea et al. 2017[54] also quantified the decrease in clearance (by 69.3% and 40.6% respectively) during TH, leading for the latter in an extension in dosing interval to 42h instead of 30h. The percentage of neonates reaching toxic trough concentrations is thereby reduced from 40-76% to 14-17%[54].

Erythropoietin, darbepoetin and 2-iminobiotin

As second-line interventions in addition to TH, certain drugs have also been investigated for their neuroprotective effect[55–57]. Erythropoietin (EPO), most well-known for its hematopoietic effect, is not only produced by the kidneys but also by brain cells (astrocytes, neurons, oligodendrocytes). EPO binds to the EPO-receptor which is expressed by these same cells as well as by microglial and endothelial cells. It is proposed to have an anti-inflammatory effect in addition to inhibition of cell death and promotion of angiogenesis and development of new neurons and oligodendrocytes[58–61]. Combining EPO with TH is therefore hypothesized to have an additive neuroprotective effect[57,62–65]. The synthetic darbepoetin mimics the effects of EPO, but has a longer half-life, enabling the use of a longer dosing interval (Table 2f). Only a very small amount (<5%) of EPO, and thus darbepoetin, is excreted unchanged by the kidneys[66]. The majority is degraded in the body, possibly by intracellular degradation, of which the exact mechanisms are for the main part unknown[67].

Wu et al. 2012[68] performed a phase I prospective study to determine the optimal dosing of EPO in humans by testing different doses ranging from 250 U to 2,500 U/kg per dose every 48 hours. This article shows that with an increase in dose, clearance decreased from 15.6 ± 6.3 to 7.7 ± 0.9 mL/kg/h. The dose of 1,000 IU/kg had the best AUC and C_{max} for the administered dose (similar to those of a study with rats)[69]. Frymoyer et al. 2017[70], who included both the phase I trial mentioned above and the subsequent phase II study, found a C_L of 8.3 mL/kg/h which is considerably lower than a study reported for premature extremely low birth weight neonates (13.1 mL/kg/h)[71]. They also concluded that neonates with HIE receiving TH will typically have a 50% higher exposure after the same EPO dose. The recommended dose used was 1,000 IU/kg every 24h for 3 doses and then 2 doses every 48h. The phase II trial found a clinical benefit of administering the EPO with significantly better brain MRI and motor function at 12 months[62]. The corresponding Phase III is momentarily still in progress.

Baserga et al. 2015[72] administered 2 doses of the EPO-derived molecule Darbe® (darbepoetin), one on day 0 and one on day 7. They divided the neonates into two treatment groups with one group receiving 2 µg/kg while the other was administered a higher dose of 10 µg/kg. A third placebo control group was needed to determine the baseline EPO as the quantification machines cannot distinguish between endogenously produced EPO and the synthetic Darbe®. The group receiving the higher dose had an AUC that best matched that of animal studies[69]. Roberts et al. 2015[73] also concluded that gestational age is inversely correlated with C_L, meaning that pre-term neonates have a higher clearance than term neonates.

2-Iminobiotin is another potential neuroprotective agent. A dose seeking (to target exposure) study in 2 consecutive cohorts of 6 neonates undergoing TH has recently been reported, and dosing for the second cohort had to be adapted to further compensate for the renal impairment associated with asphyxia. The clearance in these 12 cases was 0.38 l/h, but cannot be compared to data in non-cooled or healthy neonates[74].

DISCUSSION

Compared to the latest structured review (2015) that provided information on the pharmacokinetics during TH for 4 compounds (gentamicin, topiramate, phenobarbital, morphine), the current systematic

search provide PK data on 15 compounds, reflecting the impressive and relevant progress made in this specific field of neonatal pharmacology[75].

Based on the available data, It is difficult to compare pharmacokinetic data in HIE newborns with or without TH due to the small number of studies that include normothermic HIE controls, as TH is now standard practice in most countries. It would thus be unethical not to offer the best care (i.e. TH). Therefore, the control group are often neonates that do not suffer from HIE, which in turn makes it difficult to disentangle the effect of HIE from TH.

Phenobarbital is a relatively old anti-epileptic drug, which in adults has been substituted by newer agents. However, it remains one of the most effective anti-epileptic drugs for neonatal seizures. Pending the outcome of ongoing comparative studies on the use of phenobarbital or levetiracetam as first line anti-epileptic[76], it is possible that levetiracetam or another anti-epileptic drug will replace phenobarbital. However, as phenobarbital has an inducing effect on the metabolism of midazolam (which is often co-administered), if phenobarbital were to be replaced by levetiracetam, the dosage of midazolam needs to be reduced if we aim for similar exposure [34]. Along the same line, and because levetiracetam is mainly eliminated by renal route, it is reasonable to except a similar decrease in renal clearance as quantified for aminoglycosides [Table 2e]. Such an 'informed' approach to anticipate for the impact of renal impairment on dosing to attain a given target exposure has been described in the 2-iminobiotin paper[74].

This article only explored the impact of HIE+TH on the pharmacokinetics in neonates. But in the clinical setting, pharmacodynamics, the effect that the drug has on the body, also needs to be considered. For anti-epileptic drugs, this means the seizure control response documented by amplitude integrated EEG. The only study in which this was quantified until present, is Van den Broek et al. 2012[35] who found that administering phenobarbital to neonates undergoing TH reduced transition from continuous normal voltage to discontinuous normal voltage aEEG background level. The only other pharmacodynamic parameter evaluated is target attainment of antibiotics which was calculated using

the ƒT > MIC ratio, which is the time that the free concentration of the substance is higher than the minimal inhibitory concentration. Although Cies et al. 2017[24] administered 100 mg/kg ampicillin every 8 hours, their modelling predicted that 25 or 50 mg/kg every 24 hours would actually be sufficient to attain a target of 50% and even 100% of time above MIC. Bijleveld et al. 2018[53] also used simulations to recommend a gestational age (GA) dependent dosing regimen; 50mg/kg/d of amoxicillin for GA of 36-37w and 75mg/kg/d for GA 38-42 in three doses for 7 days, which result in target attainment of 100% for *Streptococcus agalactiae* and *Listeria monocytogenes*. The Dutch paediatric formulary currently advises a dose of 75 mg/kg/d in three doses for all neonates that are younger than 7 days postnatal age and have birth weight of over 2 kg [81].

The Dutch paediatric formulary is an illustration on how published data can subsequently be assessed and provided as specific dosing regimens to facilitate knowledge diffusion and access. Because of this assessment (one of the criteria is prospective validation, a confirmation of a suggested dosing regimen), not all published data are immediately present in this formulary (Table 3) [82]. Furthermore, therapeutic drug monitoring can be used to verify if a given drug exposure is within the therapeutic range. This mainly relates to drugs where TDM is routinely performed like phenobarbital or aminoglycosides (gentamicin, amikacin), but may be considered also for midazolam and its metabolite (prolonged sedation related to metabolite accumulation), lidocaine (cardiac effects), or topiramate (therapeutic failure if used as anti-epileptic, also relevant for phenobarbital, midazolam, lidocaine).

CONCLUSION

The aim of this paper was to determine the effect of lowering the core body temperature of the neonate with HIE, on the pharmacokinetics of different drugs used during TH. This was evaluated by comparing values for the different pharmacokinetic processes; absorption, distribution, metabolisation and elimination. Depending on drug and elimination route, TH has clinical relevant effects on PK.

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Figure 1: Flow chart on search strategy, search terms and number of hits in PubMed, Embase and Cochrane.

Figure 2: Flow diagram of data selection and subsequent results.

AUTHOR'S CONTRIBUTIONS

Isabelle Claire Lutz, MD

was responsible for the study design, conducted the literature search and was responsible for the writing process of the manuscript. She finalized the final version, and approved the final draft.

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TABLES

Table 1: Study characteristics (*= one study reported on both phenobarbital and midazolam pharmacokinetics)

Characteristic	No.
Type of study	36
Prospective observational	28
Retrospective observational	6
Mixed	2
Drug	
Anti-epileptics	9
Phenobarbital*	6
Midazolam*	3
Lidocaïne	1
Antibiotics	12
Gentamicin	8
Amikacin	1
Ampicillin	1
Amoxicillin	1
Benzyl Penicillin	1
Analgesic/sedative	3
Morphine	3
Various neuroprotective	11
Erythropoietin	2
Darbepoietin	2
Topiramate	3
Bumetanide	2
Melatonin	1
2-iminobiotin	1
Pharmacokinetic parameter	
Absorption	3
Distribution	30
Metabolic clearance	6
Excretion	35
Elimination half-life	18
Normothermic controls	
Yes	10
No	26

Table 2a-f: Overview of all selected articles.

VD = volume of distribution, CL = total body clearance, t1/2 = half-life, NT = normothermia, TH = therapeutic hypothermia, DH = deep hypothermia, MH = moderate hypothermia, PNA = postnatal age, OHM = 1-hydroxymidazolam, HMG = 1-hydroxymidazolam-glucuronide, MEGX = monoethylglycinexylidide, M3G = morphine-3-glucoronide, M6G = morphine-6-glucuronide

Table 2a: *topiramate and melatonin*

Topiramaat	n =	Study type	Absorption	V_D (L/kg)	Metabolite C_L (mL/kg/h)	C_L (mL/kg/h)	$t_{1/2}$ (h)
Filippi et al. 2009[14]	13	Prospective	AUC = 343.2 mg/L/h	/	/	MH = 13.87 DH = 15.72	MH = 29 DH = 49
Nuñez-Rqmiro et al. 2019[16]	106	Prospective (RCT)	AUC = 77.8 mg/L/h	/	/	19.7	54.1
Marques et al. 2019[17]	52	Prospective (RCT)	/	0.976	/	TH = 12.6 Post-warm = 15.3 **↓ 20.8% = ↓ 6.95%/˚C**	/
Melatonin							
Balduini et al. 2019[21] **(Melatonine)**	5	Prospective	AUC_{ss} = 9.71 µg/mL/h t_{abs} = 2.8h	1.8	/	46.0	26.4

Table 2b*: phenobarbital*

Phenobarbital	n =	Study type	Absorption	V_D (L/kg)	Metabolite C_L (mL/kg/h)	C_L (mL/kg/h)	$t_{1/2}$ (h)
Van den broek et al. 2012[35]	31	Prospective	/	0.986	/	4.914	140
Shellhaas et al 2013[37]	39	Retrospective	/	0.92	/	7.6	85
Filippi et al 2011[38]	19	Prospective	/	1.56	/	6.38	173.3
Favié et al 2019[34]	113	Prospective	/	1.03	/	2.394	298
Pokorná et al 2019[36]	40	Prospective	/	0.519	/	2.1	120
Síma et al 2015[39]	37	Prospective	/	0.48	/	3.4	93.7

Table 2c*: midazolam and lidocaine*

Midazolam	n =	Study type	Absorption	V_D (L/kg)	Metabolite C_L (mL/kg/h)	C_L (mL/kg/h)	$t_{1/2}$ (h)
Welzing et al. 2013[40]	9	Prospective	/	5.91 L (median weight not calculated)	/	154.0	7.0
Van den Broek	53	Prospective	/	1.93	OHM = 0.7	268.0	5.0

et al 2015[41]					HMG 0.02		
Favié et al. 2019[34]	118	Prospective	/	1.55	OHM = 0.969 **↓25.7% = ↓ 8.6%/˚C** HMG = 0.055	100	/
Lidocaïne							
Favié et al. 2020 [43]	159	Mixed	/	2.66	MEGX = 431	506 **↓21.8% = ↓ 7,3%/˚C**	/
Van den Broek et al. 2013[42]	48	Mixed	/	3.11	MEGX = 166	397.0 **↓24.0% = ↓ 8,0%/˚C**	5.5

Table 2d: *morphine*

Morphine	**n =**	**Study type**	**Absorption**	**V_D (L/kg)**	**Metabolite C_L (mL/kg/h)**	**C_L (mL/kg/h)**	**$t_{1/2}$ (h)**
Favié et al 2019[45]	244	Prospective	/	2.54	M3G = 0.130 M6G = 0.494 **↓14.7% = ↓ 4.91%/˚C**	259.0 **↓20.7% = ↓6.89%/˚C**	/
Róka et al 2018[44]	16	Observational	/	/	/	'could not be calculated'	/
Frymoyer et al 2016[23]	20	Prospective	/	2.286 **↓37.0% = ↓12.3%/˚C**	M3G = 0.188 M6G = 0.197	216.0 **↓46.7% = ↓15.6%/˚C**	/

Table 2e*: antibiotics*

Gentamicin	**n =**	**Study type**	**Absorption**	**V_D (L/kg)**	**Metabolite C_L (mL/kg/h)**	**C_L (mL/kg/h)**	**$t_{1/2}$ (h)**
Bijleveld et al. 2016[49]	47	Prospective	/	0.897	/	60 (day 2) 77.4 (29%↑ day 5)	/
Liu et al. 2009[46]	55	Prospective	/	/	/	/	/
Frymoyer et al. 2013[50]	29	Retrospective	/	0.47	/	36,0	/
Ting et al. 2014[47]	46	Retrospective	/	NT = 0.45 HT = 0.41	/	NT = 51.0 HT = 33.0 **↓35.3% = ↓11.7%/˚C**	NT = 7.0 HT = 9.6
Mark et al. 2013[48]	23	Retrospective	/	/	/	NT = 50.0 HT = 40.0 **↓25% = ↓8.3%/˚C**	NT = 6.6 HT = 9.2 **40%↑**
Frymoyer et al. 2013[51]	52	Retrospective	/	/	/	17.0	/
Cies et al. 2018[77]	12	Prospective	/	0.87	/	132.0	/
Martinkova et al. 2010[78]	35	Prospective	/	0.40	/	46.0	/
Other antibiotics							
Cies et al. 2017 (Ampicilline)[24]	13	Prospective	/	0.52	/	25.8	/
Bijleveld et al. 2018 (Amoxicillin)[53]	125	Prospective	/	0.34 (V_C)	/	PNA 0-4 = 90,0 PNA 5 = 14.,0 **55%↑**	/

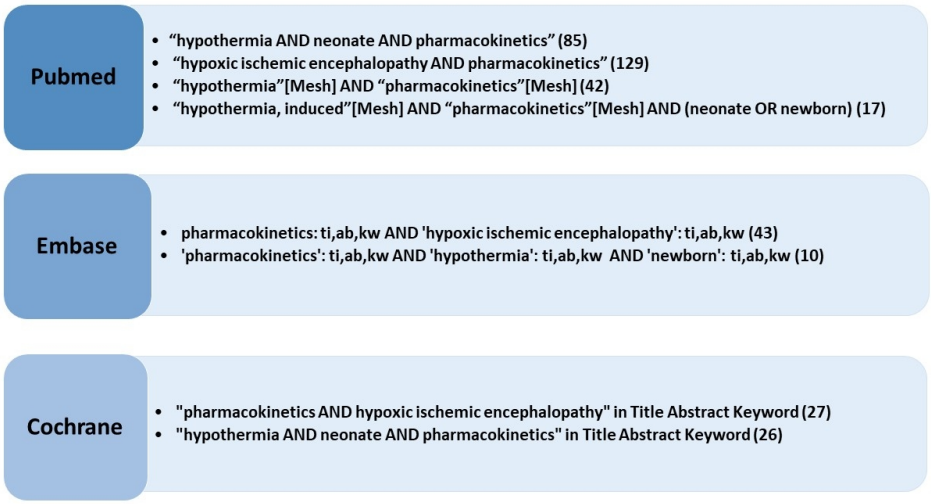
Bijleveld et al. 2018[52] **(Benzylpenicillin)**	41	Prospective	/	0.62 (V_C)	/	PNA 0-4 = 160.0 PNA 5 = 250.0 **56%↑**	/
Cristea et al. 2017 (Amikacin)[54]	56	Retrospective	/	0.832	/	49.5 **↓40.6% = ↓13.5%/˚C**	/

***Table 2f**: erythropoietin, darbepoietin, bumetanide*

Erythropoietin	n =	Study type	Absorption	V_D (L/kg)	Metabolite C_L (mL/kg/h)	C_L (mL/kg/h)	$t_{1/2}$ (h)
Frymoyer et al. 2017[70]	47	Prospective	/	V_C = 0.074 V_P = 0.096	/	8.3	/
Wu et al. 2012[68]	24	Prospective	/	0.095-0.178	/	7.7-15.6 C_L↓ with dose↑	/
Roberts et al. 2015[73]	26	Prospective	/	0.511	/	15.0	23.6
Baserga et al. 2015[72]	30	Prospective	/	/	/	40.0-50.0	24-35
Miscellaneous							
Julien et al. 2016[79] **(Bumetanide)**	14	Prospective	/	0.23	/	19.8	8.4
Pressler et al. 2015[80] **(Bumetanide)**	14	Prospective	/	0.23	/	19.8	8.4
Favié et al. 2020 [74] **(2-Iminobiotin)**	12	Prospective	/	V_C = 0.138 V_P = 0.368	/	113.8	2.9

Table 3: Dosing recommendations of drugs used in newborns with hypoxic ischemic encephalopathy undergoing hypothermia as provided at the Dutch paediatric formulary are compared to some recommendations reported in literature (Loading dose = LD, Maintenance dose = MD) [82].

	Recommendations as published		Dutch pediatric formulary	
	LD	MD	LD	MD
Phenobarbital	20 – 40 mg/kg	/	20 – 40 mg/kg	2.5 – 5 mg/kg in 1-2 doses/day
Morphine	50 µg/kg	5 µg/kg/h	50 – 100 µg/kg over 60 mins	3 – 20 µg/kg/h
Midazolam	0.05-0.1 mg/kg	0.05 – 0.1 mg/kg/h	0.05 mg/kg	0.05 – 0.1 mg/kg/h maximum 24h
Lidocaine	>2.0-2.5kg: 2 mg/kg (10 min) <2.5-4.5kg: 2 mg/kg (10 min)	6 mg/kg/h (3.5h) → 3 mg/kg/h (12h) → 1.5 mg/kg/h (12h) 7 mg/kg/h (3.5h) → 3.5 mg/kg/h (12h) → 1.75 mg/kg/h (12h)	2 mg/kg (10 min)	4 mg/kg/h (6h) → 2 mg/kg/h (12h) → stop
Topiramate	15 mg/kg	5 mg/kg/d	**Not yet validated**	**Not yet validated**
Erythropoietin	/	1.000 U/kg every 24h (3x) then every 48h (2x)	**Not yet validated**	**Not yet validated**
Darbepoetin	/	10 mcg/kg every 7d (2x)	**Not yet validated**	**Not yet validated**
Gentamicin	/	4-5 mg/kg every 36h (5x)	/	5 mg/kg every 36h
Amikacin	/	15 mg/kg every 36h	**Not yet validated**	**Not yet validated**



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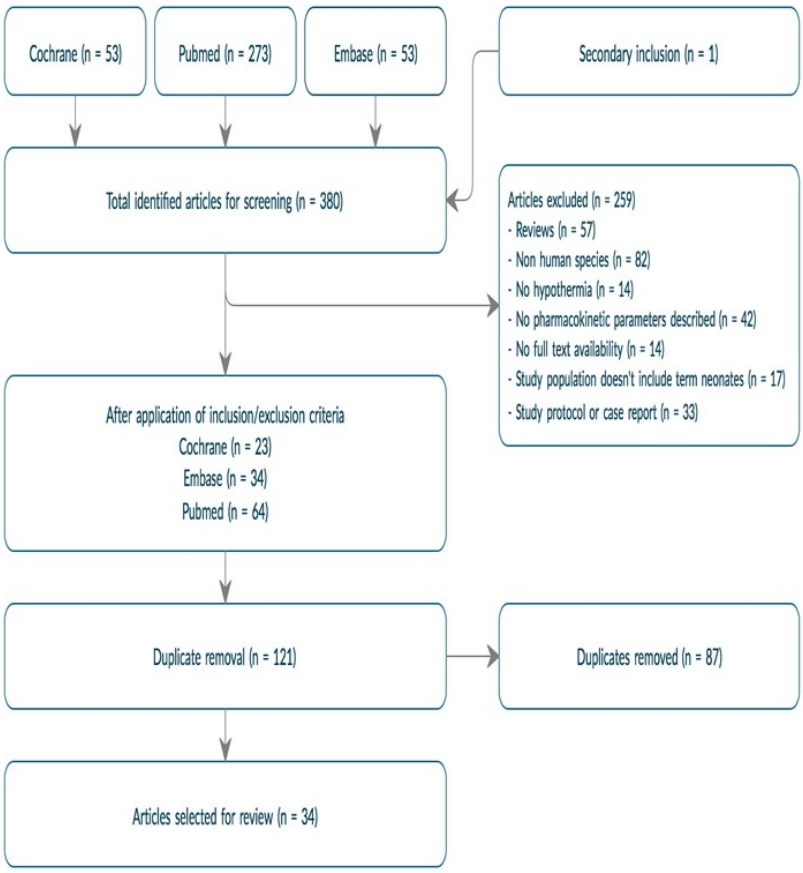

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Pharmacokinetics during therapeutic hypothermia for neonatal hypoxic ischemic encephalopathy: a literature review

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ABSTRACT

Background Neonatal hypoxic ischemic encephalopathy due to perinatal asphyxia, can result in severe neurodevelopmental disability or mortality. Hypothermia is at present the only proven neuroprotective intervention. During hypothermia, the neonate may need a variety of drugs with their specific pharmacokinetic profile. The aim of this paper is to determine the effect that hypothermia for neonates suffering from hypoxic ischemic encephalopathy has on the pharmacokinetics and to what extent dosing regimens need adjustments.

Method A systematic search was performed on Pubmed, Embase and Cochrane library of literature (2000-2020) using a combination of the following search terms; therapeutic hypothermia, neonate, hypoxic ischemic encephalopathy and pharmacokinetics. Titles and abstracts were screened, and inclusion/exclusion criteria were applied. Finally, relevant full-texts were read, and secondary inclusion was applied on the identified articles.

Results A total of 380 articles were retrieved, and 34 articles included after application of inclusion/exclusion criteria and duplicate removal, 2 additional papers were included as suggested by the reviewers. Twelve (12) out of 36 studies on 15 compounds demonstrated a significant decrease in clearance, be it that the extent differs between routes of elimination and compounds, most pronounced for renal elimination (phenobarbital no difference, midazolam metabolite -21%, lidocaine -24%; morphine -21 to -47%, gentamicin -25 to -35%, amikacin -40%) during hypothermia. The data as retrieved in literature were subsequent compared to the dosing regimen as stated in the Dutch paediatric formulary.

Conclusion Depending on the drug-specific disposition characteristics, therapeutic hypothermia in neonates with hypoxic ischemic encephalopathy affects pharmacokinetics.

What's known

Therapeutic hypothermia has a neuroprotective effect for neonates with hypoxic ischemic hypothermia.

Hypoxic ischemic asphyxia and lowering the core body temperature has impact on the pharmacokinetics, up to the level that dosing regimens for these neonates should be adapted.

What's new

Compared to the latest structured review (2015) on pharmacokinetics during hypothermia for 4 compounds (gentamicin, topiramate, phenobarbital, morphine), the current systematic search provides data on 15 compounds, reflecting the relevant progress made.

A significant decrease in clearance is observed in neonates during therapeutic hypothermia, be it that the extent differs between routes of elimination and compounds, but most pronounced for renal elimination (phenobarbital no difference, midazolam metabolite -21%, lidocaine -24%; morphine -21 to -47%, gentamicin -25 to -35%, amikacin -40%) during hypothermia.

INTRODUCTION

Neonatal hypoxic ischemic encephalopathy (HIE), brain damage sustained as a result of perinatal asphyxia, occurs in 1.5 out of 1000 births[1] and can result in severe neurodevelopmental disability or mortality in respectively 24.9% and 34.1% of cases[2]. Perinatal asphyxia is a condition characterised by a persistently low APGAR-score (≤5) assessed at 5 and 10 minutes after birth, or metabolic acidosis, defined as a pH of <7.0 and/or base deficit of ≥16 mmol/L, measured in the foetal umbilical artery or arterial blood within 1 hour after birth[3,4]. The HIE severity can be categorised by the Sarnat score into mild, moderate and severe brain injury based on the abnormality of level of consciousness, spontaneous activity, posture, tone, primitive reflexes and autonomic function[5]. Alternatively, the Thompson score is another scoring system that uses similar criteria like Sarnat but also includes the presence of seizures and fontanelle tension; Both scores can be used for prognosis and provide prognostic value and quantify HIE into mild, moderate and severe [6].

Therapeutic hypothermia (TH) is at present the only proven effective intervention for moderate and severe HIE. It significantly reduces the mortality by 8.8% and severe morbidity by 15.4% (relative risk = 0.75; number needed to treat = 7)[2]. In its current approach, TH aims to cool the body temperature of the neonate to 33.5˚C for the duration of 72 hours within 6 hours after birth, and a subsequently gradual rewarming at a rate of 0.3-0.5˚C per hour[7–10]. According to the current guidelines all (near)-term neonates who meet the criteria for perinatal asphyxia and are classified as moderate or severe HIE by the Thompson score should receive this treatment [5,6].

During the hypothermic period the neonate may need a variety of different drugs ranging from anti-epileptic drugs to sedatives or antibiotics. Simultaneously, different substances with different mechanisms involved are investigated on their additive neuroprotective effect. We refer the interested reader to a recent review on the pharmacodynamics of these claimed neuroprotective compounds[11]

However, for any drug administered to these patients, the pharmacokinetic profile may be altered by the physical state of the neonate with HIE and TH. This is due to the altered pathophysiology explained by both the disease (asphyxia) and the intervention (TH), and includes renal impairment, altered haemodynamics like cardiac output and blood flow, or altered hepatic function [12]. The aim of this paper is to provide an overview on the effects of TH in neonates suffering from HIE have on the pharmacokinetics of drugs administered during this hypothermic period, and whether dosing regimens need to be adjusted.

METHODS

A systematic search was performed on Pubmed, Embase and Cochrane library of all literature between 1 January 2000 and 1 January 2020. A combination of the following search terms was hereby used: "therapeutic hypothermia, neonate, hypoxic ischemic encephalopathy and pharmacokinetics". In PubMed the corresponding MeSH terms for these search terms were used. An overview of the performed search and the subsequent results is provided in Figure 1.

Only articles with full-text availability written in English were included. Another inclusion criterion was the reporting of a pharmacokinetic parameter for at least one of the following processes: absorption, distribution, metabolism or excretion. Only studies that concerned the human species were included. Reviews and study protocols that provided no new information, were excluded after screening references for secondary inclusion. Articles were excluded if the study population did not include term neonates or if TH was not applied.

First the titles of all articles were screened. If the relevance was unsure, the abstract was subsequently read. Finally, the resulting selected articles were thoroughly studied, and the references screened for secondary inclusion.

Patient and Public Involvement

This research was conducted without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

RESULTS

A schematic overview of the entire data selection process can be found in Figure 2. By using the above-mentioned search terms, a total of 380 publications were identified for screening, secondary inclusion included. The exact number of studies for each of the performed searches can be found in Figure 1. After application of the inclusion and exclusion criteria and removal of duplicates, the remaining 34 articles were deemed eligible for inclusion. To keep the overview updated, two additional papers (2-iminobiotin, lidocaine) that were not in the initial search strategy, but were suggested by the reviewers were added in the revised version of the paper (both very recent publications, not in the initial search).

Characteristics of all retained (n=36) articles are provided in Table 1. Most of the studies were prospective multicentre observational studies. The drugs reviewed ranged from those that are the current standard treatment for the occurrence of neonatal seizures (i.e. phenobarbital), to various substances that have been hypothesised to have a neuroprotective effect in newborns suffering from HIE. Some pharmacokinetic parameters were much more frequently analysed than others. Total body clearance (C_L) was calculated in all but one of the articles, whereas absorption was only relevant in three analyses as most of the drugs are administered by intravenous route. Only 10 out of 36 articles included a normothermic control group in the study design. More common, the quantification of the effect of TH on pharmacokinetics was based on data pooling or literature data, and subsequent use of population pharmacokinetic modelling approaches.

In an attempt to facilitate comparison of the pharmacokinetic parameters for absorption, distribution, metabolism and excretion described in the selected articles, the quantification of these parameters can be found in Tables 2a-f. Because of the different characteristics of each drug administered during

the hypothermic period, the included studies as presented in Tables 2a-f were sorted by drug to facilitate comparison. In the subsequent synthesis, the effect of TH on each of the pharmacokinetic parameters will be discussed, illustrated by available findings for different drugs.

Absorption

The rate and amount of absorption of a drug determines the maximum plasma concentration (C_{max}) and time needed to reach this peak concentration (t_{max}). Absorption can best be assessed by bioavailability, which can be calculated based on the area under the curve after oral (AUC_{PO}) versus intravenous (AUC_{IV}) administration, using the following formula: AUC_{PO}/AUC_{IV} x 100%. There are many factors that influence absorption after oral administration such as gastric emptying, food and physico-chemical characteristics of the drug. These factors can be different in neonates when compared to adults, so that for example differences in gastric emptying rate will affect the t_{max} for drugs that are mainly absorbed in the duodenum [13]. However, absorption parameters are less relevant in the context of TH as all drugs except for topiramate and melatonin are administered intravenously, where a bioavailability of 100% can be assumed.

Topiramate

Topiramate has been hypothesised to improve the neuroprotective effect of TH, with glutamate-receptor inhibition as underlying claimed mechanism [14]. In adults, it has a high oral bioavailability (±80%)[15]. As topiramate is usually not used in children younger than 2 years, there were no available pharmacokinetic data on in neonates. In all three articles, the first dose of topiramate was 5 mg/kg and was administered via nasogastric tube [14,16,17]. The two more recent studies went on to decrease the dose to 3 mg/kg for days 2-5 [16,17], whereas Filippi et al. 2009[14] continued with 5 mg/kg for 3 days (Table 2a). Both dosing regimens resulted in a steady state within the therapeutic range of 5-20 mg/L but steady state was only reached after 48 hours. Filippi et al. 2009[14] made a distinction between mild hypothermia (33-34˚C) and deep hypothermia (30-33˚C) to assess if the depth

of hypothermia had an impact on pharmacokinetics. Although no significant differences were found between the observed plasma concentrations and the calculated parameters, a lower AUC_{0-24} and steady state plasma concentration (C_{avg}), and a longer elimination half-life were observed in the deep hypothermia group. Due to the small sample size the differences were not statistically significant, however, it is possible that these effects would become statistically significant in a larger study population. Nuñez-Ramiro et al. 2019[16] and Marques et al. 2019[17] both used the same dosing strategy, but only the first research group calculated the AUC_{0-24}, which was considerably lower than the one calculated by Filippi[14] (see Table 2a). Both groups concluded that a 5 mg/kg loading dose (LD) and 3 mg/kg as a maintenance dose (MD) was too low and the time needed to reach therapeutic concentrations too long [14,16]. Since there is a strong correlation between serum level and seizure control or neuroprotective effects, it is desirable to reach steady state more quickly. The pharmacokinetic modelling suggests that a LD of 15 mg/kg followed by a MD of 5 mg/kg would lead to 90% of patients reaching therapeutic concentrations after 24 hours [14,16,17]. Though the AUC was calculated in 2/3 studies, this parameter does not only depend on absorption, but is also affected by subsequent distribution, metabolism and elimination. Unfortunately, in the absence of intravenous PK data in neonates, quantification of bioavailability and the impact of asphyxia and TH cannot be assessed.

Melatonin

The hormone melatonin which regulates circadian rhythm, is produced by the pineal gland. In several animal models of HIE it has been shown to augment the neuroprotective efficacy of hypothermia by inhibiting apoptosis, stimulating anti-oxidant enzymes and by modulating the inflammatory response [18–20]. Balduini et al. 2019[21] are the first to have conducted a study with melatonin in human neonates with only 5 infants included, in order to study the pharmacokinetics (Table 2a). The authors administered melatonin by continuous drip over naso-/orogastric tube at 0.5 mg/kg over 4 hours, after which the absorption time was estimated to be 2.8 hours [21]. Larger clinical studies to evaluate the efficacy of melatonin in neonates with HIE are therefore needed.

Distribution

Distribution is typically expressed as volume of distribution (V_D) which represents a virtual space that the drug has been dissolved in. V_D not only depends on substance characteristics but also patient factors which can be different between neonates and adults. For example, neonates have a proportional higher body water content which can imply that the V_D per kg is higher for water-soluble compounds[22].

Out of the 36 articles included in this analysis, 30 reported on aspects of the V_D, sometimes based on a central (V_c) and peripheral (V_P) distribution volume. However, only 2/30 articles described a significant impact of the TH on distribution. Interestingly, Frymoyer et al. 2017 describe a 37% decrease in the V_D of morphine (8.0 L in TH versus 12.7 L for normothermia for an infant with mean birth weight of 3.5 kg), whereas Cies et al. 2017 on the other hand found a 30% increase of V_D for Ampicillin[23,24]. Both studies compared their own data to earlier reported studies in literature, instead of a dataset of normothermic controls integrated in the same analysis [25,26].

Clearance: metabolization and excretion

After absorption and distribution, drugs are slowly cleared from the body by one of three ways; (1) excretion, unchanged by the kidneys, (2) elimination via other excretion routes such as bile, sweat, saliva or milk glands, and/or (3) metabolization mainly by the liver into metabolite(s) that can be both an inactive substance or a more active molecule compared to the mother compound. Such metabolites commonly subsequently undergo additional metabolism or are eliminated by renal or other excretion routes. Quantitatively, the largest group of metabolizing enzymes is the cytochrome-P450-mono-oxygenase family (CYP450). Tortorici et al. 2007[27] established that hypothermia impacted hepatic drug elimination by decreasing the activity of the CYP450 system, based on studies in brain-injured adults and healthy volunteers. However, such findings need to be intergrated with iso-enzyme specific ontogeny in neonates[12]. The sum of excretion in the urine of both the intact substance and

metabolites that have been produced by the liver, further metabolization and excretion into bile, sweat, saliva or milk, make up the total body clearance (C_L) [12].

If for example a substance is primarily cleared by excretion in the urine, renal function is the principal determinate of clearance. The Cochrane systematic review on TH could not observe any significant differences in urine output in neonates who underwent TH compared to those who did not. Furthermore, meta-analysis showed that TH did not cause a significant difference in the occurrence of acute kidney injury[2]. This suggests that asphyxia, and not the intervention is the major determinant of altered renal elimination clearance. In the first week after birth there is maturation in renal function, the rate of which depends on the gestational age at birth, with premature neonates displaying a slower maturation than term neonates[28]. Creatinine is a degradation product of creatine which is produced by the muscles at a near constant speed and subsequently filtered passively by the kidneys into the urine. Consequently, under normal circumstances it is a good biomarker for renal clearance, however studies show that birth creatinine reflects maternal creatinine values to subsequently peak in the first 48 hours of life irrespective from the presence of acute kidney injury related to asphyxia[12,29,30]. Therefore, serum creatinine might not be a good indicator of renal clearance for neonates in the first days after birth[31,32]. In total, 13 out of 36 studies demonstrated a significant decrease in total clearance as high as 46% during TH (Tables 2a-2f).

Phenobarbital

Neonatal seizures in the context of HIE are treated in first-line with phenobarbital, an anti-epileptic drug that in adults has been replaced by other anti-epileptic agents with fewer adverse effects. Phenobarbital is metabolized in the liver mostly by CYP2C9 to inactive metabolites, which are then renally excreted together with 25% of unchanged phenobarbital[33]. None of the included studies measured the serum levels of phenobarbital metabolites so no final conclusions can be drawn about metabolism[34-39]. About 66% of neonates with HIE and seizures respond to phenobarbital[34,35]. Pokorná et al. 2019[36] observed decreased clearance during TH, although these changes were not

statistically significant (Table 2b). Similarly, none of the other included studies were able to detect a substantial effect of TH on the pharmacokinetic parameters measured[34,35,37–39]. The therapeutic window for phenobarbital is 20-40 mg/L, which can be attained with a LD of 20 mg/kg that can be increased up to a maximum of 40 mg/kg if seizure control is not attained[35,38]. However a more recent study suggests to start at a higher dose of 30 mg/kg[34]. Some of the authors also continued with a MD ranging from 1.5 mg/kg to 8 mg/kg after the LD depending on the study[36,38]. Other factors that were investigated for an effect on pharmacokinetic parameters were the severity of HIE and the influence of other drug[36]. The severity was found to have an effect on phenobarbital clearance, likely because of a decreased cardiac output which leads to less blood flow to the kidneys and liver and a reduction in metabolic capacity. This suggest that disease severity is a more prominent covariate of phenobarbital clearance compared to TH[36]. Furthermore, concomitant dobutamine administration also had an effect on phenobarbital clearance (although the authors suspect this was an artefact of the small sample size[39]).

Midazolam

A model compound of a drug metabolised by a CYP450 enzyme is midazolam, converted by CYP3A to 1-hydroxymidazolam (OHM) and successively to 1-hydroxymidazolam-glucuronide (HMG), both of which are sedative and further excreted by renal route. Midazolam is used as an add-on anti-epileptic drug when seizure control with phenobarbital monotherapy is inadequate and provides an additional 23% of patients with seizure control. Intriguingly, none of the studies on midazolam showed an effect of TH on midazolam clearance[34,40,41]. However, Favié et al. reported on a significant reduction of the clearance of HMG (8.6%/˚C), likely reflecting the impact of renal impairment [34,40,41] (Table 2c). Midazolam is usually concomitantly used with phenobarbital, which is an inducer of CYP3A. This effect has been quantified, so that midazolam metabolic clearance is increased by 2.33-fold during co-medication with phenobarbital[34].. Thus, if another anti-epileptic drug is used as a first-line agent instead of phenobarbital, the dose of midazolam should be reduced by about 50%[34]. A point of attention is the occurrence of hypotension during treatment with midazolam as blood pressure and

plasma concentrations of midazolam have a direct relationship, with blood pressure dropping by 3.6 mmHg for every increase in plasma concentration of 0.1 mg/L[41].

Lidocaine

If there is still no seizure control after adding midazolam, lidocaine can be added as a third-line treatment, which is effective in 91% of the patients where seizure control could not be achieved with phenobarbital and midazolam alone [42,43]. Lidocaine is a drug frequently used as a local anaesthetic or anti-arrhythmic agent and is predominantly metabolised by CYP3A into the active monoethylglycinexylidide (MEGX) and subsequently glycine xylidide (GX), which is an inactive metabolite. The clearance of lidocaine was shown to be decreased by 24% (or 8,0%/˚C) during TH[42]. The extent of the impact of TH on lidocaine pharmacokinetics has recently been confirmed (decrease 21%, 7.26%/°C) in a further extended cohort of patients, including 49 neonates undergoing TH (prospective validation)[43].

Morphine [23,44,45]

Morphine is metabolised in the liver into two metabolites by the enzyme UDP-glucoronosyltransferase 2B7 (UGT2B7): morphine-3-glucoronide (M3G) and morphine-6-glucuronide (M6G). Both morphine and its less abundant metabolite M6G are analgesic and sedative, whereas M3G is inactive. Róka et al 2008[44] concluded that the clearance of morphine and its metabolites were decreased during TH (Table 2d). This conclusion was based on differences in median morphine plasma concentration [292 ng/mL (137–767 ng/mL) during TH to 206 ng/mL (88–327 ng/mL) in normothermic neonates (P = 0.014)] even though the normothermic newborns on average had received a higher dose of morphine. Unfortunately, the authors were unable to report on morphine pharmacokinetics. It is therefore not possible to compare the results with the subsequent studies. However, it did raise the question of altered clearance under TH and inspired others. Frymoyer et al [23] compared the pharmacokinetic parameters observed in their prospective study during TH to the data provided by Knibbe et al 2009[25] during normothermia. They concluded that morphine clearance was decreased by 46.7%

(15.6%/˚C) in newborns treated with TH [23]. An interesting finding in this study was that M6G accumulation is dependent on the serum creatinine. Monte-Carlo simulations suggested that a LD of 50 µg/kg followed by a MD of 5 µg/kg or intermittent dosing of 40-50 µg/kg every 6 hours is recommended to stay within the therapeutic window[23]. The results of these simulations were seconded by the findings of two open label prospective studies conducted in the Netherlands reported by Favié et al 2019[45]. They found a decreased morphine clearance of 20.7% (or 6.98%/˚C) and of metabolites M3G and M6G of 14.7% (or 4.91%/˚C) during TH. The authors subsequently observed that over the subsequent first five days of life there is an increase in clearance, the phenotypic final result of maturation of UGT2B7 activity, disease recovery and finalization of TH.

Antibiotics

Gentamicin is an aminoglycoside antibiotic administered empirically to most neonates with HIE and is predominantly eliminated renally. Ideally the dose should generate a peak concentration of 10-12 mg/L and a trough concentration not exceeding 2 mg/L as this could cause oto- and nephrotoxicity. Liu et al. 2009[46] were the first to study the effect of TH on gentamicin pharmacokinetics (Table 2e). They compared trough concentrations between normothermic and hypothermic group, which were not significantly different, but were, with a dose of 4-5 mg/kg every 24h, above 2 mg/L in 36-44% of neonates. They did however not calculate or measure other pharmacokinetic parameters but set the scene for better pharmacokinetic studies [46]. Two retrospective studies observed a decrease by 25.0-35.3% (or 8.3-11.7%/˚C) in the C_L in neonates undergoing TH, and a significant increase in $t_{1/2}$[47,48]. Another study found an increase of 29% in clearance on postnatal age day 5, which can be considered as steady state normothermia after rewarming[49].

With regards to gentamicin dosing, many different schemes have been explored with an increasing interval between doses, ranging from 2.5 mg/kg every 12h[47] to 4 mg/kg every 24h[48] to 4-5mg/kg every 36h[48–51]. Just increasing the dosing interval from 24h to 36h reduced the number of newborns with trough concentrations under 2 mg/L from 62% to 96% without compromising on the

percentage reaching the peak concentration[51]. But whatever dosing regimen is used, all studies recommend therapeutic drug monitoring (TDM), and the same holds true for other aminoglycosides (like amikacin)[49].

Apart from gentamicin, other antibiotics have also been investigated: ampicillin, amoxicillin, amikacin and benzylpenicillin [24,52,53,54]. The Pharmacool study group observed a 55-56% increase in clearance of amoxicillin and benzylpenicillin after postnatal age day 5, which can be considered as reaching normothermic steady state[52,53]. Based on subsequent simulations, the authors suggest implementing a gestational age (GA) dependent dosing regimen, with a lower dose for GA of 36-37 weeks. Both Cies et al. [24] and Cristea et al. [54] also quantified the decrease in clearance (by 69.3% and 40.6% respectively) during TH, leading for the latter in an extension in dosing interval to 42h instead of 30h. The percentage of neonates reaching toxic trough concentrations is thereby reduced from 40-76% to 14-17%[54].

Erythropoietin, darbepoetin and 2-iminobiotin

As second-line interventions in addition to TH, certain drugs have also been investigated for their neuroprotective effect[55–57]. Erythropoietin (EPO), most well-known for its hematopoietic effect, is not only produced by the kidneys but also by brain cells (astrocytes, neurons, oligodendrocytes). EPO binds to the EPO-receptor which is expressed by these same cells as well as by microglial and endothelial cells. It is proposed to have an anti-inflammatory effect in addition to inhibition of cell death and promotion of angiogenesis and development of new neurons and oligodendrocytes[58–61]. Combining EPO with TH is therefore hypothesized to have an additive neuroprotective effect[57,62–65]. The synthetic darbepoetin mimics the effects of EPO, but has a longer half-life, enabling the use of a longer dosing interval (Table 2f). Only a very small amount (<5%) of EPO, and thus darbepoetin, is excreted unchanged by the kidneys[66]. The majority is degraded in the body, possibly by intracellular degradation, of which the exact mechanisms are for the main part unknown[67].

Wu et al. 2012[68] performed a phase I prospective study to determine the optimal dosing of EPO in humans by testing different doses ranging from 250 U to 2,500 U/kg per dose every 48 hours. This article shows that with an increase in dose, clearance decreased from 15.6 ± 6.3 to 7.7 ± 0.9 mL/kg/h. The dose of 1,000 IU/kg had the best AUC and C_{max} for the administered dose (similar to those of a study with rats)[69]. Frymoyer et al. 2017[70], who included both the phase I trial mentioned above and the subsequent phase II study, found a C_L of 8.3 mL/kg/h which is considerably lower than a study reported for premature extremely low birth weight neonates (13.1 mL/kg/h)[71]. They also concluded that neonates with HIE receiving TH will typically have a 50% higher exposure after the same EPO dose. The recommended dose used was 1,000 IU/kg every 24h for 3 doses and then 2 doses every 48h. The phase II trial found a clinical benefit of administering the EPO with significantly better brain MRI and motor function at 12 months[62]. The corresponding Phase III is momentarily still in progress.

Baserga et al. 2015[72] administered 2 doses of the EPO-derived molecule Darbe® (darbepoetin), one on day 0 and one on day 7. They divided the neonates into two treatment groups with one group receiving 2 µg/kg while the other was administered a higher dose of 10 µg/kg. A third placebo control group was needed to determine the baseline EPO as the quantification machines cannot distinguish between endogenously produced EPO and the synthetic Darbe®. The group receiving the higher dose had an AUC that best matched that of animal studies[69]. Roberts et al. 2015[73] also concluded that gestational age is inversely correlated with C_L, meaning that pre-term neonates have a higher clearance than term neonates.

2-Iminobiotin is another potential neuroprotective agent[74]. A dose seeking (to target exposure) study in 2 consecutive cohorts of 6 neonates undergoing TH has recently been reported, and dosing for the second cohort had to be adapted to further compensate for the renal impairment associated with asphyxia. The median clearance in these 12 cases was 0.38 l/h, but cannot be compared to data in non-cooled or healthy neonates[74].

DISCUSSION

Compared to the latest structured review (2015) that provided information on the pharmacokinetics during TH for 4 compounds (gentamicin, topiramate, phenobarbital, morphine), the current systematic search provide PK data on 15 compounds, reflecting the impressive and relevant progress made in this specific field of neonatal pharmacology since 2015[75].

Based on the available data, it is difficult to compare pharmacokinetic data in HIE newborns with or without TH due to the small number of studies that include normothermic HIE controls, as TH is now standard practice in most countries. It would thus be unethical not to offer the best care (i.e. TH). Therefore, the control group are often neonates that do not suffer from HIE, which in turn makes it difficult to disentangle the effect of HIE from TH[12].

Phenobarbital is a relatively old anti-epileptic drug, which in adults has been substituted by newer agents. However, it remains one of the most effective anti-epileptic drugs for neonatal seizures[34-39]. Pending the outcome of ongoing comparative studies on the use of phenobarbital or levetiracetam as first line anti-epileptic[76], it is possible that levetiracetam or another anti-epileptic drug will replace phenobarbital. However, as phenobarbital has an inducing effect on the metabolism of midazolam (which is often co-administered), if phenobarbital were to be replaced by levetiracetam, the dosage of midazolam needs to be reduced if we aim for similar exposure [34]. Along the same line, and because levetiracetam is mainly eliminated by renal route, it is reasonable to except a similar decrease in renal clearance as quantified for aminoglycosides [Table 2e, 46-51,54,77,78]. Such an 'informed' approach to anticipate for the impact of renal impairment on dosing to attain a given target exposure has been described in the 2-iminobiotin paper[74].

This article only explored the impact of HIE+TH on the pharmacokinetics in neonates. But in the clinical setting, pharmacodynamics, the effect that the drug has on the body, also needs to be considered. For anti-epileptic drugs, this means the seizure control response documented by amplitude integrated EEG [35]. The only study in which this was quantified until present, is Van den Broek et al. 2012[35] who found that administering phenobarbital to neonates undergoing TH reduced transition from continuous normal voltage to discontinuous normal voltage aEEG background level. The only other pharmacodynamic parameter evaluated is target attainment of antibiotics which was calculated using the ƒT > MIC ratio, which is the time that the free concentration of the substance is higher than the minimal inhibitory concentration[24,53]. Although Cies et al. 2017[24] administered 100 mg/kg ampicillin every 8 hours, their modelling predicted that 25 or 50 mg/kg every 24 hours would actually be sufficient to attain a target of 50% and even 100% of time above MIC. Bijleveld et al. 2018[53] also used simulations to recommend a gestational age (GA) dependent dosing regimen; 50mg/kg/d of amoxicillin for GA of 36-37w and 75mg/kg/d for GA 38-42 in three doses for 7 days, which result in target attainment of 100% for *Streptococcus agalactiae* and *Listeria monocytogenes*. The Dutch paediatric formulary currently advises a dose of 75 mg/kg/d in three doses for all neonates that are younger than 7 days postnatal age and have birth weight of over 2 kg [81].

The Dutch paediatric formulary is an illustration on how published data can subsequently be assessed and provided as specific dosing regimens to facilitate knowledge diffusion and access. Because of this assessment (one of the criteria is prospective validation, a confirmation of a suggested dosing regimen), not all published data are immediately present in this formulary (Table 3) [82]. Furthermore, therapeutic drug monitoring can be used to verify if a given drug exposure is within the therapeutic range. This mainly relates to drugs where TDM is routinely performed like phenobarbital or aminoglycosides (gentamicin, amikacin), but may be considered also for midazolam and its metabolite (prolonged sedation related to metabolite accumulation), lidocaine (cardiac effects), or topiramate (therapeutic failure if used as anti-epileptic, also relevant for phenobarbital, midazolam, lidocaine)[12,75].

CONCLUSION

The aim of this paper was to determine the effect of lowering the core body temperature of the neonate with HIE, on the pharmacokinetics of different drugs used during TH. This was evaluated by comparing values for the different pharmacokinetic processes; absorption, distribution, metabolisation and elimination. Depending on drug and elimination route, TH has clinical relevant effects on PK.

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Table 2a-f: Overview of all selected articles.

Table 3: Dosing recommendations of drugs used in newborns with hypoxic ischemic encephalopathy undergoing hypothermia as provided at the Dutch paediatric formulary are compared to some recommendations reported in literature (Loading dose = LD, Maintenance dose = MD) [82].

Figure 1: Flow chart on search strategy, search terms and number of hits in PubMed, Embase and Cochrane.

Figure 2: Flow diagram of data selection and subsequent results.

AUTHOR'S CONTRIBUTIONS

Isabelle Claire Lutz, MD

was responsible for the study design, conducted the literature search and was responsible for the writing process of the manuscript. She finalized the final version, and approved the final draft.

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TABLES

Table 1: Study characteristics (*= one study reported on both phenobarbital and midazolam pharmacokinetics; **= elimination half-life reflects both distribution and metabolic clearance/excretion)

Characteristic	No.
Type of study	36
Prospective observational	28
Retrospective observational	6
Mixed	2
Drug	
Anti-epileptics	9
Phenobarbital*	6
Midazolam*	3
Lidocaïne	1
Antibiotics	12
Gentamicin	8
Amikacin	1
Ampicillin	1
Amoxicillin	1
Benzyl Penicillin	1
Analgesic/sedative	3
Morphine	3
Various neuroprotective	11
Erythropoietin	2
Darbepoietin	2
Topiramate	3
Bumetanide	2
Melatonin	1
2-iminobiotin	1
Pharmacokinetic parameter	
Absorption	3
Distribution volume	30
Metabolic clearance	6
Excretion	35
Elimination half-life**	18
Normothermic controls	
Yes	10
No	26

Table 2a-f: Overview of all selected articles.

VD = volume of distribution, CL = total body clearance, t1/2 = half-life, NT = normothermia, TH = therapeutic hypothermia, DH = deep hypothermia, MH = moderate hypothermia, PNA = postnatal age, OHM = 1-hydroxymidazolam, HMG = 1-hydroxymidazolam-glucuronide, MEGX = monoethylglycinexylidide, M3G = morphine-3-glucoronide, M6G = morphine-6-glucuronide

Table 2a: *topiramate and melatonin*

Topiramaat	n =	Study type	Absorption	V_D (L/kg)	Metabolite C_L (mL/kg/h)	C_L (mL/kg/h)	$t_{1/2}$ (h)
Filippi et al. 2009[14]	13	Prospective	AUC = 343.2 mg/L/h	/	/	MH = 13.87 DH = 15.72	MH = 29 DH = 49
Nuñez-Rqmiro et al. 2019[16]	106	Prospective (RCT)	AUC = 77.8 mg/L/h	/	/	19.7	54.1
Marques et al. 2019[17]	52	Prospective (RCT)	/	0.976	/	TH = 12.6 Post-warm = 15.3 **↓ 20.8% = ↓ 6.95%/˚C**	/
Melatonin							
Balduini et al. 2019[21] **(Melatonine)**	5	Prospective	AUC_{ss} = 9.71 µg/mL/h t_{abs} = 2.8h	1.8	/	46.0	26.4

Table 2b*: phenobarbital*

Phenobarbital	n =	Study type	Absorption	V_D (L/kg)	Metabolite C_L (mL/kg/h)	C_L (mL/kg/h)	$t_{1/2}$ (h)
Van den broek et al. 2012[35]	31	Prospective	/	0.986	/	4.914	140
Shellhaas et al 2013[37]	39	Retrospective	/	0.92	/	7.6	85
Filippi et al 2011[38]	19	Prospective	/	1.56	/	6.38	173.3
Favié et al 2019[34]	113	Prospective	/	1.03	/	2.394	298
Pokorná et al 2019[36]	40	Prospective	/	0.519	/	2.1	120
Síma et al	37	Prospective	/	0.48	/	3.4	93.7

2015[39]							

***Table 2c**: midazolam and lidocaine*

Midazolam	**n =**	**Study type**	**Absorption**	**V_D (L/kg)**	**Metabolite C_L (mL/kg/h)**	**C_L (mL/kg/h)**	**$t_{1/2}$ (h)**
Welzing et al. 2013[40]	9	Prospective	/	5.91 L (median weight not calculated)	/	154.0	7.0
Van den Broek et al 2015[41]	53	Prospective	/	1.93	OHM = 0.7 HMG 0.02	268.0	5.0
Favié et al. 2019[34]	118	Prospective	/	1.55	OHM = 0.969 **↓25.7% = ↓ 8.6%/˚C** HMG = 0.055	100	/
Lidocaïne							
Favié et al. 2020 [43]	159	Mixed	/	2.66	MEGX = 431	506 **↓21.8% = ↓ 7,3%/˚C**	/
Van den Broek et al. 2013[42]	48	Mixed	/	3.11	MEGX = 166	397.0 **↓24.0% = ↓ 8,0%/˚C**	5.5

***Table 2d:** morphine*

Morphine	**n =**	**Study type**	**Absorption**	**V_D (L/kg)**	**Metabolite C_L (mL/kg/h)**	**C_L (mL/kg/h)**	**$t_{1/2}$ (h)**
Favié et al 2019[45]	244	Prospective	/	2.54	M3G = 0.130 M6G = 0.494 **↓14.7% = ↓ 4.91%/˚C**	259.0 **↓20.7% = ↓6.89%/˚C**	/
Róka et al 2018[44]	16	Observational	/	/	/	'could not be calculated'	/
Frymoyer et al 2016[23]	20	Prospective	/	2.286 **↓37.0% = ↓12.3%/˚C**	M3G = 0.188 M6G = 0.197	216.0 **↓46.7% = ↓15.6%/˚C**	/

***Table 2e**: antibiotics*

Gentamicin	**n =**	**Study type**	**Absorption**	**V_D (L/kg)**	**Metabolite C_L (mL/kg/h)**	**C_L (mL/kg/h)**	**$t_{1/2}$ (h)**
Bijleveld et al. 2016[49]	47	Prospective	/	0.897	/	60 (day 2) 77.4 (29%↑ day 5)	/
Liu et al. 2009[46]	55	Prospective	/	/	/	/	/
Frymoyer et al. 2013[50]	29	Retrospective	/	0.47	/	36,0	/
Ting et al. 2014[47]	46	Retrospective	/	NT = 0.45 HT = 0.41	/	NT = 51.0 HT = 33.0 **↓35.3% = ↓11.7%/˚C**	NT = 7.0 HT = 9.6
Mark et al. 2013[48]	23	Retrospective	/	/	/	NT = 50.0 HT = 40.0 **↓25% = ↓8.3%/˚C**	NT = 6.6 HT = 9.2 **40%↑**
Frymoyer et al. 2013[51]	52	Retrospective	/	/	/	17.0	/
Cies et al. 2018[77]	12	Prospective	/	0.87	/	132.0	/

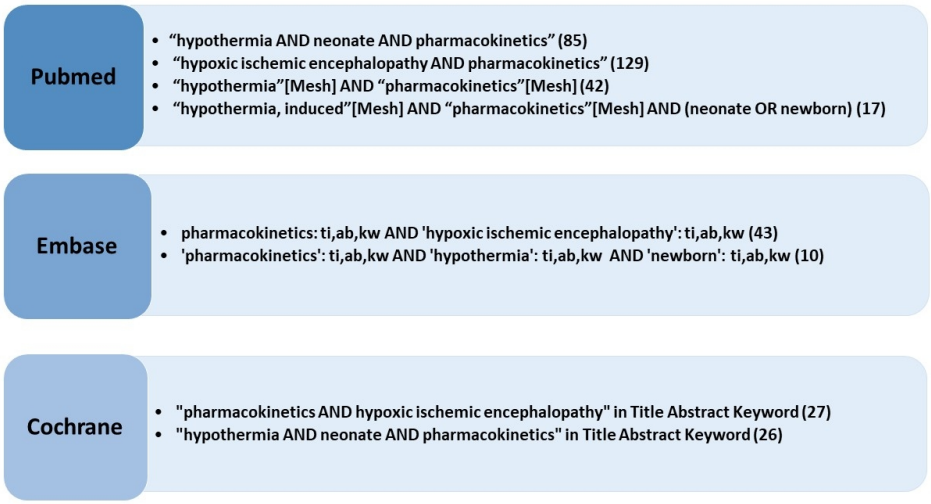
Martinkova et al. 2010[78]	35	Prospective	/	0.40	/	46.0	/
Other antibiotics							
Cies et al. 2017 (Ampicilline)[24]	13	Prospective	/	0.52	/	25.8	/
Bijleveld et al. 2018 (Amoxicillin)[53]	125	Prospective	/	0.34 (V_C)	/	PNA 0-4 = 90,0 PNA 5 = 14.,0 **55%↑**	/
Bijleveld et al. 2018[52] **(Benzylpenicillin)**	41	Prospective	/	0.62 (V_C)	/	PNA 0-4 = 160.0 PNA 5 = 250.0 **56%↑**	/
Cristea et al. 2017 (Amikacin)[54]	56	Retrospective	/	0.832	/	49.5 **↓40.6% = ↓13.5%/˚C**	/

***Table 2f**: erythropoietin, darbepoietin, bumetanide*

Erythropoietin	n =	Study type	Absorption	V_D (L/kg)	Metabolite C_L (mL/kg/h)	C_L (mL/kg/h)	$t_{1/2}$ (h)
Frymoyer et al. 2017[70]	47	Prospective	/	V_C = 0.074 V_P = 0.096	/	8.3	/
Wu et al. 2012[68]	24	Prospective	/	0.095-0.178	/	7.7-15.6 C_L↓ with dose↑	/
Roberts et al. 2015[73]	26	Prospective	/	0.511	/	15.0	23.6
Baserga et al. 2015[72]	30	Prospective	/	/	/	40.0-50.0	24-35
Miscellaneous							
Julien et al. 2016[79] **(Bumetanide)**	14	Prospective	/	0.23	/	19.8	8.4
Pressler et al. 2015[80] **(Bumetanide)**	14	Prospective	/	0.23	/	19.8	8.4
Favié et al. 2020 [74] **(2-Iminobiotin)**	12	Prospective	/	V_C = 0.138 V_P = 0.368	/	113.8	2.9

Table 3: Dosing recommendations of drugs used in newborns with hypoxic ischemic encephalopathy undergoing hypothermia as provided at the Dutch paediatric formulary are compared to some recommendations reported in literature (Loading dose = LD, Maintenance dose = MD) [82].

	Recommendations as published		Dutch pediatric formulary	
	LD	MD	LD	MD
Phenobarbital	20 – 40 mg/kg	/	20 – 40 mg/kg	2.5 – 5 mg/kg in 1-2 doses/day
Morphine	50 µg/kg	5 µg/kg/h	50 – 100 µg/kg over 60 mins	3 – 20 µg/kg/h
Midazolam	0.05-0.1 mg/kg	0.05 – 0.1 mg/kg/h	0.05 mg/kg	0.05 – 0.1 mg/kg/h maximum 24h
Lidocaine	>2.0-2.5kg: 2 mg/kg (10 min) <2.5-4.5kg: 2 mg/kg (10 min)	6 mg/kg/h (3.5h) → 3 mg/kg/h (12h) → 1.5 mg/kg/h (12h) 7 mg/kg/h (3.5h) → 3.5 mg/kg/h (12h) → 1.75 mg/kg/h (12h)	2 mg/kg (10 min)	4 mg/kg/h (6h) → 2 mg/kg/h (12h) → stop
Topiramate	15 mg/kg	5 mg/kg/d	**Not yet validated**	**Not yet validated**
Erythropoietin	/	1.000 U/kg every 24h (3x) then every 48h (2x)	**Not yet validated**	**Not yet validated**
Darbepoetin	/	10 mcg/kg every 7d (2x)	**Not yet validated**	**Not yet validated**
Gentamicin	/	4-5 mg/kg every 36h (5x)	/	5 mg/kg every 36h
Amikacin	/	15 mg/kg every 36h	**Not yet validated**	**Not yet validated**



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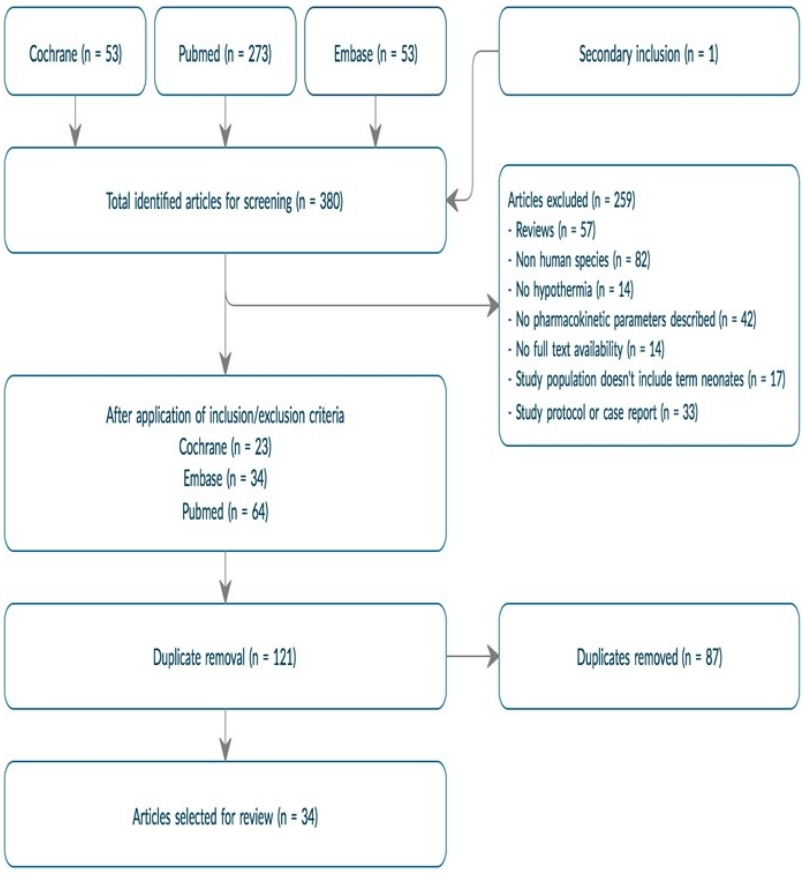

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