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REVIEW ARTICLE

# Pharmacotherapy for Seizures in Neonates with Hypoxic Ischemic Encephalopathy

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**Abstract** Seizures are common in neonates with moderate and severe hypoxic ischemic encephalopathy (HIE) and are associated with worse outcomes, independent of HIE severity. In contrast to adults and older children, no new drugs have been licensed for treatment of neonatal seizures over the last 50 years, because of a lack of controlled clinical trials. Hence, many antiseizure medications licensed in older children and adults are used off-label for neonatal seizure, which is associated with potential risks of adverse effects during a period when the brain is particularly vulnerable. Phenobarbital is worldwide the first-line drug and is considered standard of care, although there is a limited evidence base for its efficacy. Second-line agents include phenytoin, benzodiazepines, levetiracetam, and lidocaine. These drugs are discussed in more detail along with two emerging drugs (bumetanide and topiramate). More safety, pharmacokinetic, and efficacy data are needed from well-designed clinical trials to develop safe and effective antiseizure regimes for the treatment of neonatal seizures in HIE.

**Key Points**

Seizures are common in the neonatal period, with up to 60% of neonatal seizures caused by hypoxic ischemic encephalopathy in the term infant.

Phenobarbital is used worldwide as a first-line drug for neonatal seizures despite there being a limited evidence base for its efficacy.

Second-line agents used for neonatal seizures include phenytoin, benzodiazepines, levetiracetam, and lidocaine, all of which are used off-label.

## 1 Introduction

At an incidence of 1–5 per 1000 live births, seizures are the most common neurological emergency in full-term newborns [1, 2]. As many as 60% of neonatal seizures present as a result of hypoxic ischemic encephalopathy (HIE), a form of brain injury typically resulting from perinatal asphyxia [3]. Many of these seizures resolve once the underlying etiology is corrected or the acute event subsides. The neonatal brain is dynamic and therefore vulnerable to acute seizures and subsequent epileptogenesis. In HIE, neonatal seizures may exacerbate the injury caused from hypoxic ischemia. Experimental models suggest that the combination of hypoxic ischemia and drug-induced seizures increases hippocampal brain damage compared with the damage seen in those with hypoxic ischemic injury alone [4, 5]. Clinical studies have shown HIE to

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result in progressive decline in mitochondrial aerobic metabolism and subsequent loss of high-energy phosphate compounds [6, 7].

Seizures, regardless of etiology, are independently associated with increased morbidity and mortality. Moreover, seizures in the setting of HIE are associated with poor neurodevelopmental outcome, independent of HIE severity [8], more severe hippocampal cell death [9], and elevated serum concentrations of interleukin-8, an inflammatory cytokine that increases seizure susceptibility and induces organ damage [10].

## 2 Diagnosis

Challenges in diagnosis are a major obstacle to treatment of neonatal seizures. Clinical diagnosis is not reliable because seizures in neonates are often subclinical (sometimes named silent, occult, or electrographic-only seizures) and because manifestations are often difficult to distinguish from other movements in babies [10–12]. Furthermore, the phenomenon of electroclinical dissociation or uncoupling means that clinical seizure will become subclinical following drug administration [13]. The gold standard for diagnosis is continuous electroencephalogram (cEEG) video monitoring [14]. In clinical settings where cEEG is not available, amplitude integrated EEG (aEEG) may be used. This is not acceptable for drug development, as up to 30% of seizures are missed with aEEG and movement may cause false positive errors [15, 16].

## 3 Treatment

Most neonatal seizures are acute reactive seizures rather than an epileptic syndrome. An important distinction should be made between the two: neonates may have acute seizures secondary to HIE, but not epilepsy, which is characterized by two or more unprovoked seizures [17]. Antiseizure medications are typically used for management of neonatal seizures (meaning they suppress seizures), not for the prevention/cure of epilepsy.

Numerous surveys on current practice have shown that phenobarbital is used as the first-line drug worldwide, while the choice of second-line drug varies between and within countries [18–23]. Apart from phenobarbital, no drug is currently licensed for use in neonates, because of the absence of double-blind, placebo-controlled trials. Consequently, many of the same antiseizure medications given to older children and adults are used off-label for neonatal seizure [24]. The American Academy of Pediatrics advised that "the off label use of a drug should be based on sound scientific evidence, expert medical judgment, or published literature" [25]. There is also a paucity of research examining pharmacological management of seizures exclusively in neonates with HIE, and what data are available are often based on animal models or retrospective case studies. Considering the potential for these drugs to produce adverse effects during a period when the brain is particularly vulnerable, more safety, pharmacokinetic, and efficacy data are needed. Neonates with HIE represent an especially difficult population to treat. Perinatal systemic ischemia often causes significant damage outside the nervous system, resulting in multi-organ dysfunction [26], which can affect metabolism of many common drugs, making the safety of their use in this population even more uncertain.

Over the last 15 years, three systematic reviews on the efficacy of antiseizure medication for neonatal seizures have been published [27–29] in addition to a systematic review of the pharmacokinetics [30]. All of these agree that there is little or no evidence from well-conducted, randomized, controlled trials for the use of any antiseizure drugs for seizures in this age group. This has not changed over the last few years (Table 1).

In the World Health Organization (WHO) guidelines on neonatal seizures [29], four recommendations regarding treatment were formulated despite the acknowledged weak evidence. In summary, it is recommended that phenobarbital should be used as the first-line agent for the treatment of neonatal seizures (strong recommendation). However, only a weak recommendation was made concerning the choice of the second-line agent, suggesting that benzodiazepines, phenytoin, or lidocaine could be used if seizures persist despite maximal tolerated doses of phenobarbital. These drugs plus a few more recently emerging antiseizure agents are discussed in more detail (Table 2).

### 3.1 Phenobarbital

Phenobarbital is a long-acting barbiturate that has long been considered the standard first-line agent for neonatal seizures, likely due to its success in suppressing seizures in children and adults [19]. It is considered standard of care. Since therapeutic hypothermia (cooling) has become standard of care for HIE, many studies have examined the use of phenobarbital in combination with hypothermia for seizure control and neuroprotection. Its neuroprotective benefits have been described in animal [31] and clinical studies of HIE [32].

#### *3.1.1 Mode of Action*

Phenobarbital enhances gamma-aminobutyric acid A receptor ($GABA_A$) inhibitory activity, and may limit glutamate excitation [33]. It is thought that there is an

**Table 1** Evidence base to date for efficacy of antiseizure drug use in newborn babies

| | Case studies with >10 cases | Retrospective studies/prospective trial without cEEG | Prospective trial with cEEG/RCT with insufficient power | RCT |
|---|---|---|---|---|
| Phenobarbital | | Pathak et al. [57] | Bye and Flanagan [56] | Painter et al. [43] |
| | | Boylan et al. [45] | Boylan et al. [95] | |
| | | Connell et al. [137] | | |
| Phenytoin | | Pathak et al. [57] | Bye and Flanagan [56] | Painter et al. [43] |
| | | Connell et al. [137] | | |
| Midazolam | Sheth et al. [62] | Castro Conde et al. [63] | Boylan et al. [95] | None |
| | | van Leuven et al. [66] | | |
| | | Yamamoto et al. [138] | | |
| | | Shany et al. [65] | | |
| Clonazepam | | Andre et al. [139] | Bye and Flanagan [56] | None |
| Diazepam | | Connell et al. [137] | None | None |
| Lorazepam | Deshmukh et al. [67] | Maytal et al. [140] | | None |
| Levetiracetam | Rakshasbhuvankar et al. [81] | Khan et al. [86] | Abend et al. [80] | None |
| | | Ramantani et al. [141] | | |
| | | Khan et al. [142] | | |
| | | Venkatesan et al. [82] | | |
| Lidocaine | | Hellstrom-Westas et al. [94] | Boylan et al. [95] | None |
| | | Malingre et al. [96] | | |
| | | Yamamoto et al. [138] | | |
| | | Shany et al. [65] | | |
| | | Lundqvist et al. [97] | | |
| | | van den Broek et al. [93] | | |
| | | Weeke et al. [98] | | |
| Bumetanide | Kahle et al. [112] | | Pressler et al. [113] | None |
| Topiramate | | Glass et al. [124] | None | None |

*cEEG* continuous electroencephalogram, *RCT* randomized controlled trial

excitatory effect of GABA activity in the immature brain. Animal studies have revealed varied levels of $Cl^-$ transporters in different brain regions, resulting in differing intracellular $Cl^-$ concentrations. Specifically, thalamic neurons generally maintain low $Cl^-$ concentrations and will be inhibited by GABA receptor activation, while concentrations are relatively high in cortical neurons. These cells, therefore, are excited by GABA activity [34]. This research suggests that other brain regions may also maintain low $Cl^-$ concentrations despite their immaturity, and that phenobarbital could suppress seizures depending on the site of seizure genesis in the neonatal brain. However, recent studies have questioned whether this is a real phenomenon in vivo [35].

### *3.1.2 Pharmacokinetics*

Phenobarbital is metabolized by the liver and excreted via the kidneys; therefore these processes may be impaired in neonates with hepatic or renal dysfunction after HIE. The drug is 40–60% bound to plasma proteins.

Comparisons of phenobarbital treatment in neonates with or without birth asphyxia reveal differences in drug processing, namely reduced clearance and higher minimum blood concentrations [36, 37]. Clinical investigations of asphyxiated newborns have found clearance values of $4.1 \pm 1.0$ mL/kg/h [36], 0.0034 L/h/kg [38], and $0.08 \pm 0.03$ mL/min/kg [39], suggesting that these patients require only about half the maintenance dose of non-asphyxiated newborns to achieve similar blood concentrations. The potential effect of hypothermia on phenobarbital pharmacokinetics is also controversial [40, 41]. In a prospective study of asphyxiated newborns monitored by aEEG, van den Broek and co-workers [42] found no clinically relevant effect of hypothermia on phenobarbital pharmacokinetics. Others have demonstrated changes in pharmacokinetics [40] with elevated plasma concentrations and longer half-lives compared to normothermic newborns,

**Table 2** Summary of mode of action, PK, efficacy and safety of antiseizure drugs use in newborn babies

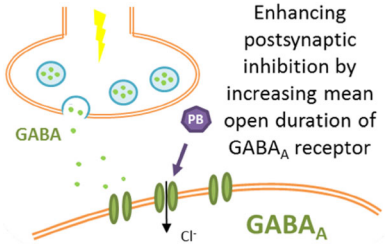
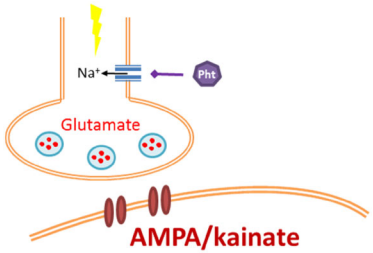
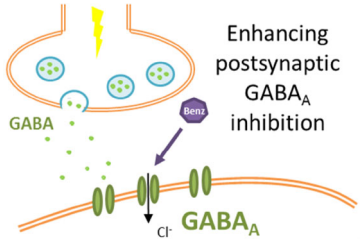
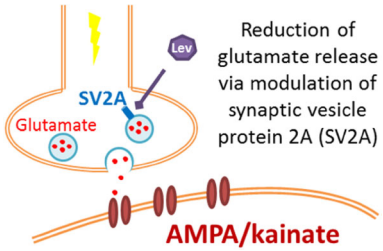
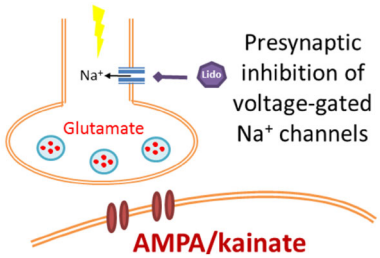
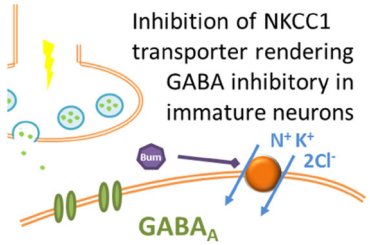
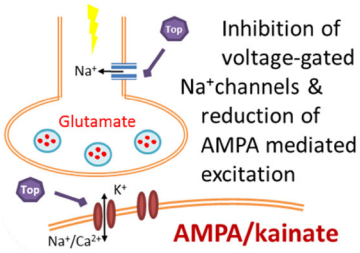
| Mode of action | PK data | Adverse events | Efficacy | Dose |
|---|---|---|---|---|
| Phenobarbital [21, 23, 27–30, 43–45, 95] | | | | |
|  | Metabolism: hepatic<br>$T$½ 80–160 h<br>Clearance reduced in HIE<br>Effect of TH on PK possible | CNS: sedation, irritability<br>Respiratory depression<br>Hypotension<br>Hepatotoxicity<br>Possible adverse neurodevelopmental outcome | First-line drug worldwide and standard of care<br>2 RCT: efficacy in 43–50%<br>Increase of electroclinical dissociation | LD: 20 mg/kg, repeat if required<br>MD: 5 mg/kg/day<br>Route: IV, IM, PO |
| Phenytoin [43, 53, 55–58] | | | | |
|  | Metabolism: hepatic<br>$T$½ 6–200 h (mean 100 h) in 1st week, 5–10 h in weeks 2–4<br>First-order kinetics<br>Drug interactions ++ | Irritation at injection site (less with fosphenytoin)<br>Sedation<br>Cardiovascular toxicity (arrhythmias)<br>Hypotension | Used as second-line, but limited evidence (1 RCT)<br>Variable efficacy: 10–50%<br>Increase of electroclinical dissociation | LD: 15–20 mg/kg IV<br>Over 20 min<br>MD: 4–8 mg/kg/day IV<br>Fosphenytoin: phenytoin (Pht) equivalent 1.5 mg/kg<br>Route: IV, PO |
| Midazolam [60, 62–66, 69, 70, 95, 137] | | | | |
|  | Metabolism: hepatic<br>$T$½ 6–14 h<br>Pharmacologically active metabolites<br>Drug interactions + | Sedation, also agitation<br>Respiratory depression<br>Hypotension<br>Myoclonus<br>Possible adverse neurodevelopmental outcome | Second-line drug<br>No RCT<br>Uncontrolled studies with variable efficacy (midazolam 0–100%) | LD: 0.05–0.15 mg/kg over 10 min<br>MD: 0.15–0.5 mg/kg/h (up to 1.0 in 1 study)<br>Route: IV |
| Levetiracetam [78–86, 138] | | | | |
|  | $T$½ 18 h in 1st week, 9 h in weeks 2–4<br>Clearance is renal and lower in 1st week of life<br>Drug interactions − | Sedation<br>Irritability<br>In older children adverse effect on behavior, and rarely hepatotoxicity | Second line<br>No RCT<br>Uncontrolled studies with variable efficacy (30–86%) | LD: 10–50 mg/kg<br>MD: 30–50 mg/kg/day<br>Route: IV, PO |

**Table 2** continued

| Mode of action | PK data | Adverse events | Efficacy | Dose |
|---|---|---|---|---|
| Lidocaine [65, 92–101] | | | | |
|  | Metabolism: hepatic<br>$T\frac{1}{2}$ 5.2–5.4 h<br>Effect of TH on PK<br>Active metabolites<br>Drug interaction + (phenytoin) | Cardiac toxicity, particularly arrhythmias<br>Sedation<br>Hypotension<br>Proconvulsive in high doses | Second line<br>No RCT<br>Uncontrolled studies with efficacy in 60–78%, less in preterm infants | LD: 2 mg/kg<br>MD: 5–7 mg/kg/h for 4 h, then reduce over 24 h<br>Adapt dose for birth weight and TH<br>Route: IV |
| Bumetanide [105, 108, 112, 113, 118, 119] | | | | |
|  | Metabolism: mostly hepatic, also renal<br>$T\frac{1}{2}$ 6–8 h<br>Clearance influenced by birth weight | Dehydration with hypotension<br>Electrolyte disturbances<br>Hyperglycemia<br>Hearing loss | No evidence of efficacy in neonatal seizures | Dose as diuretic drug: 0.01–0.05 mg/kg<br>Dose as antiseizure drug unknown<br>Route: IV, PO |
| Topiramate [117–129] | | | | |
|  | $T\frac{1}{2}$ 36 h<br>Clearance is mostly renal<br>Linear steady state PK<br>PK affected by TH<br>Drug interaction + | Sedation<br>Irritability<br>Feeding problems<br>Metabolic acidosis<br>Cognitive effects in older children | Animal data: neuroprotective properties, but not confirmed in humans<br>No evidence of efficacy in neonatal seizures | No neonatal dose<br>In infants >1 month:<br>5–25 mg/kg/day<br>Route: PO (no IV preparation) |

*Benz* benzodiazepines, *Bum* bumetanide, *CNS* central nervous system, $GABA_A$ gamma-aminobutyric acid A receptor, *HIE* hypoxic ischemic encephalopathy, *IM* intramuscular, *IV* intravenous, *LD* loading dose, *Lev* levetiracetam, *Lido* lidocaine, *MD* maintenance dose, *PK* pharmacokinetics, *PO* per os (by mouth), *RCT* randomized controlled trial, $T\frac{1}{2}$ half-life, *TH* therapeutic hypothermia, *Top* topiramate

although hypothermia may not affect phenobarbital clearance or volume of distribution [41].

#### 3.1.3 Efficacy

Phenobarbital is also the only drug strongly recommended in the WHO guideline, notably with very low evidence [29]. Phenobarbital has been shown to be incompletely effective in treatment of neonatal seizures resulting from varied etiologies, controlling seizures in only 43% of babies monitored electrographically [43]. Other studies have demonstrated control of clinical seizures in up to 70% of subjects [44], but trials specifically of newborns with HIE are more scarce. There is evidence that phenobarbital increases the electroclinical dissociation [45], possibly due to differences in cortical versus subcortical GABAergic signaling [34].

A blood concentration reference range for phenobarbital of around 10–40 mg/L has been recommended [46], and a broad scope of blood levels has been reported as sufficient to control neonatal seizures resulting from any etiology. Titration of doses to achieve levels up to 40–60 mg/L can be necessary in refractory cases. Seizures were controlled only when blood phenobarbital concentrations reached 17 mg/L in one study [47], while other studies have found blood concentrations of 12–30 mg/L to sufficiently manage neonatal seizures [48]. Much higher concentrations have been used for neonatal seizures [44, 49], but the efficacy of phenobarbital appears to plateau at concentrations around 40–45 mg/L. Resistant seizures should be treated with a second-line anticonvulsant instead of increasing the concentration of phenobarbital further [44, 50]. Phenobarbital can increase electroclinical dissociation [13].

#### 3.1.4 Dosing

The usual loading dose of phenobarbital is 20 mg/kg given intravenously, and may be repeated if needed. The initial maintenance dose is 3–5 mg/kg/day, which can be given orally or intravenously. It is available for oral use in tablet and elixir form as well as in vials of sterile solution for parenteral use.

#### 3.1.5 Adverse Events

Phenobarbital has an adequate safety profile for use in asphyxiated neonates. Intravenous administration of 40 mg/kg phenobarbital over 1 h did not adversely affect heart rate, respiratory rate, blood pressure, or blood gas values [32]. Painter and colleagues [43] also report that free plasma phenobarbital concentrations of 25 mg/L were not associated with similar complications. However, adverse events of irritability, sedation, hypotension, respiratory suppression or hepatotoxicity can occur and should be appropriately monitored for. Animal studies have indicated that phenobarbital may lead to neuronal apoptosis at blood levels used for seizure control [51], raising concerns about its possible effect on the developing brain. It has been shown that exposure to phenobarbital is associated with worse neurodevelopmental outcomes at 2 years of age when compared to levetiracetam [52].

#### 3.1.6 Summary

Phenobarbital remains the standard first-line pharmacotherapy for neonatal seizures resulting from HIE, even though data indicate it is only effective in 50–60%. It is safe for use in this population.

### 3.2 Phenytoin

Phenytoin is a sodium channel blocker. The phenytoin precursor, fosphenytoin, may be an alternative to phenytoin when used intravenously because of reduced irritation at the injection site as well as lowered incidence of cardiac arrhythmias. Phenytoin is a successful anticonvulsant similar to phenobarbital in efficacy against seizures [43].

#### 3.2.1 Mode of Action

Phenytoin acts by stabilizing sodium channels and reducing electrical conductance across the membrane. It acts on excessive neuronal firing as opposed to barbiturates. Phenytoin stimulates the $Na^+$ pump and inhibits the passive $Na^+$ influx, which prolongs the inhibitory postsynaptic potentials (IPSPs). It also inhibits the $Ca^{2+}$ influx.

#### 3.2.2 Pharmacokinetics

Ninety-five percent of the drug is metabolized by the liver and is protein bound. Both enzyme inhibiting and inducing co-medication can affect its plasma concentration. Phenytoin demonstrates first order kinetics at very low plasma concentrations and zero order at high concentrations, and these nonlinear pharmacokinetics make it difficult to determine an appropriate phenytoin dosage in neonates [53, 54]. Half-life is variable in the neonatal period, with a range of 6–200 h and longer in the first week (up to 200 h) compared to weeks 2–4 (5–10 h) [55].

#### 3.2.3 Efficacy

In a randomized, crossover study, phenobarbital controlled seizures in 43%, where phenytoin controlled seizures in 45% [43]. Another study assessed electrographic response to phenobarbital (40 mg/kg) followed by phenytoin

(15–20 mg/kg) [56]. Seizure cessation was achieved in five of the 32 patients (16%) within 120 min following the addition of phenytoin. This is similar to a prospective study without EEG [57]. Phenytoin can increase electroclinical dissociation [13].

#### 3.2.4 Dosing

The usual loading dose of 15–20 mg/kg given intravenously is recommended for fosphenytoin. Maintenance dosing is 4–8 mg/kg/day. A typical therapeutic dose range for phenytoin is 10–20 mg/L. It is available in many forms, including chewable tablets, extended release capsules, oral suspension, and injection solution. However, with oral administration, it may be difficult to achieve appropriate and stable therapeutic plasma concentrations [58].

#### 3.2.5 Adverse Effects

Common dose-related effects described in older children and adults include nystagmus and tremor; in neonates, hypotension, bradycardia and sedation have been described. Phenytoin can cause drug-induced allergic reactions such as a life-threatening dermatological (Stevens-Johnson syndrome or toxic epidermal necrolysis) and hematological conditions, but this has not been described in neonates. Cardiac toxicity is related to rapid infusion rate and has not been reported in neonates. Phenytoin's precursor, fosphenytoin, may be used as an alternative because it produces less irritation at the injection site.

#### 3.2.6 Summary

Phenytoin/fosphenytoin is an important antiseizure medication to use in this population. It is mostly used as second-line medication, although there is evidence for efficacy from one randomized controlled trial [43]. However, few other studies have confirmed the efficacy of phenytoin [56, 57, 137].

### 3.3 Benzodiazepines

Benzodiazepines are GABA agonists at the $GABA_A$ receptors; this resuls in sedative-hypnotic, anxiolytic and muscle relaxant effects. Diazepam, lorazepam, clobazam, midazolam, and clonazepam are commonly employed for treating neonatal seizures. Midazolam is the most frequently used in neonates in the acute setting.

#### 3.3.1 Mode of Action

Benzodiazepines act at the $GABA_A$ receptor [59] by increasing the affinity of GABA and its receptor, which increases the opening frequency of the $GABA_A$ receptor to suppress the spread of ictal discharge. The $GABA_A$ receptor is a ligand-gated, chloride-selective ion channel.

#### 3.3.2 Pharmacokinetics

Benzodiazepines have a rapid onset of action and a short duration of effect. The half-life is typically 3.3-fold longer and the clearance is 3.7-fold smaller in healthy neonates than in adults [60]. Clearance of midazolam is lower in neonates than in older children and adults [61]. Multiple organ failures as well as the presence of disease reduce its clearance. Mechanical ventilation prolongs its half-life [60]. Most benzodiazepines are highly protein bound. They are oxidatively metabolized by the cytochrome P450 enzymes (phase I), conjugated with glucuronide (phase II), and excreted almost entirely in the urine. The function of cytochrome P450 increases throughout the first year of life.

#### 3.3.3 Efficacy

Some retrospective studies suggested excellent efficacy of midazolam [62, 63], but this was not confirmed in other retrospective studies [64, 65]. In a prospective study that looked at midazolam in HIE term babies, it was found that following phenobarbital and lidocaine, a load of midazolam followed by maintenance revealed seizure cessation within 24 h in 11 of 15 subjects (73%). No significant side effects were reported [66]. When a single dose of lorazepam was added to phenobarbital and phenytoin in seven infants, three of the neonates with cEEG monitoring had seizure cessation within 5 min following lorazepam [67]. Diazepam efficacy is less than that of phenobarbital [68].

#### 3.3.4 Dosing

Dosing recommendations vary. Midazolam's loading dose is between 0.05 and 0.15 mg/kg; it is followed by a maintenance dose of 0.05 mg/kg/h and is increased as needed up to a maximum of 0.4 mg/kg/h given intravenously. Diazepam is administered IV at a dose of 0.1–0.5 mg/kg (via slow push) or rectally at a dose of 0.5 mg/kg/dose. Lorazepam can also be given in the acute setting, at a dose of 0.05–0.1 mg given intravenously (via slow push) with a repeat dose of 0.05 mg in 10 min.

#### 3.3.5 Adverse Effects

Since benzodiazepines are typically used in the acute setting, it is important to consider that disease may affect their pharmacokinetics in neonates. Respiratory depression and hypotension appear in a limited number of babies who receive intravenous injection. It is more common when

used with narcotics or when administered by rapid bolus. Hypotension is more common with continuous infusion. Pain, tenderness, and thrombophlebitis have occurred following injection of midazolam. Particularly in preterm infants, myoclonus has been observed in association with midazolam treatment [69]. More recently, concerns have been raised that use of benzodiazepines in the neonatal period may negatively impact brain development [70].

#### 3.3.6 Summary

Benzodiazepines are best used in the acute setting and are typically discontinued prior to the patient's discharge from hospital. They are relatively safe when monitored appropriately and are typically used in refractory cases to first-line treatment.

### 3.4 Levetiracetam

Levetiracetam has efficacy as both monotherapy [71] and adjunctive therapy for patients as young as 4 years of age [72]. Despite limited data on children less than 1 year of age, off-label use is employed. It may be administered as either a tablet or intravenous formulation. Despite a lack of efficacy data from randomized controlled trials, it is used as first-line medication for neonatal seizures in several centers, particularly in Germany and Switzerland.

#### 3.4.1 Mode of Action

Levetiracetam is mechanistically different to most antiseizure medications, and its complete mode of action is still not fully understood. It appears to exert its effect presynaptically by impeding synaptic vesicle trafficking. The binding target of levetiracetam is synaptic vesicle protein 2A (SV2A), which is expressed throughout all brain regions and is involved in exocytosis of neurotransmitters [73, 74].

#### 3.4.2 Pharmacokinetics

Levetiracetam has a very favorable pharmacokinetic profile; it is characterized by >95% bioavailability, is not protein bound to plasma protein, rapidly achieves steady-state concentration (24–48 h), and is not metabolized by the cytochrome P450 system. Clearance occurs through renal systems, with 66% excreted unchanged in the urine and 34% metabolized primarily by hydrolysis in the blood [75–77]. Consequently, dosage adjustments should be considered in patients with renal dysfunction, because total body clearance is likely decreased. There are currently no published data of levetiracetam pharmacokinetics in neonates with exclusively HIE-induced seizures. Available data for babies with seizures from any etiology reveal that the clearance, half-life, and volume of distribution were increased in neonates compared to older children [78, 79].

#### 3.4.3 Efficacy

A lack of randomized controlled trials makes the efficacy of levetiracetam difficult to assess for this population. The data available are mostly from retrospective case studies and indicate levetiracetam has good efficacy as a second-line medication for seizures refractory to phenobarbital. Case studies have demonstrated seizure reduction or seizure freedom after receiving levetiracetam in the acute setting [80–83]. However, one study has suggested that levetiracetam may be less efficacious for neonatal seizures after severe HIE than for those with seizures from other etiologies [84]. Overall efficacy ranges from 30 to 86% in uncontrolled studies [82, 85]. Three randomized controlled trials are now underway to test its efficacy as a first-line drug in neonatal seizures (clinical trials NCT01720667, NCT03107507, and NCT02550028).

#### 3.4.4 Adverse Events

Several retrospective studies have reported no levetiracetam-related adverse events [80–82, 84, 86]. Specifically, no adverse respiratory, cardiovascular, hematological, renal, or hepatic effects were observed. Experimental studies have shown that exposure to levetiracetam does not increase apoptosis in white matter of examined brain regions compared to saline-treated rats [87]. Animal studies suggest that levetiracetam may be neuroprotective against apoptotic cell death after hypoxia [88], although this is controversial [89]. Mildly low platelet counts have been reported following levetiracetam treatment in one prospective study [79]. Other commonly reported side effects in the pediatric population are somnolence and behavioral changes, particularly irritability [78, 84, 90, 91].

#### 3.4.5 Summary

Given its favorable pharmacokinetic, efficacy, and safety data, levetiracetam is a contender for a second-line medication when seizures are refractory to phenobarbital. Its use in this population is, however, limited by a lack of controlled clinical trials assessing its efficacy and pharmacokinetics specifically in newborns with HIE. There are two ongoing clinical trials which will report on efficacy, safety, and pharmacokinetics (NCT01720667; NCT02550028), including a phase II randomized, blinded, controlled trial comparing levetiracetam to phenobarbital as a first-line medication (NCT01720667). However, neither of these trials are limited to babies with HIE.

### 3.5 Lidocaine

Lidocaine is an amide used as a local anesthetic and antiarrhythmic drug, but it also has a concentration-dependent effect on seizures. At lower concentrations, lidocaine can effectively suppress seizures, whereas at high concentrations it may cause seizures. It is a popular antiseizure drug in some European countries (Sweden, The Netherlands, etc.) where it is widely used as a second- or third-line choice.

#### *3.5.1 Mode of Action*

Lidocaine suppresses seizures through inhibition of voltage-gated $Na^+$ channels in presynaptic neurons. Due to its lipophilic property, it quickly passes the brain–blood barrier.

#### *3.5.2 Pharmacokinetics*

Lidocaine is a 'high-clearance' drug, meaning that the hepatic clearance of lidocaine is determined by the hepatic blood flow and therefore reduced during hypothermia [92, 93]. The half-life is 5.2–5.4 h.

#### *3.5.3 Efficacy*

Several retrospective and uncontrolled studies indicate an efficacy between 70 and 92% of neonates responding to lidocaine as a second-line antiseizure drug [65, 94–98]. However, most of these studies used aEEG rather than cEEG and were retrospective. No randomized control trials with lidocaine exist to confirm efficacy in a controlled setting.

#### *3.5.4 Dosing*

The dose needs to be adjusted to bodyweight and in case of therapeutic hypothermia. This will ensure lower cumulative dosages and consequently reduce the risk of adverse cardiac effects. A dosing regimen was developed by Malingre et al. [96] and was more recently updated by van den Broek at al. [93] to reduce the risk of these dose dependent events:

- In *normothermic* conditions: initial bolus loading dose of 2 mg/kg over 10 min. For infants with bodyweights of 2.0–2.5 kg, this is followed by continuous infusions of 6 mg/kg/h for 4 h, then 3 mg/kg/h for 12 h, and finally 1.5 mg/kg/h for 12 h before stopping. For infants with bodyweights of 2.5–4.5 kg, the bolus is followed by 7 mg/kg/h for 4 h, then 3.5 mg/kg/h for 12 h, and finally 1.75 mg/kg/h for 12 h before stopping.
- In *hypothermic* conditions: initial bolus loading dose of 2 mg/kg over 10 min. For infants with bodyweights of 2.0–2.5 kg, this is followed by continuous infusions of 6 mg/kg/h for 3.5 h, then 3 mg/kg/h for 12 h, and finally 1.5 mg/kg/h for 12 h before stopping. For infants with bodyweights of 2.5–4.5 kg, the bolus is followed by 7 mg/kg/h for 3.5 h, then 3.5 mg/kg/h for 12 h, and finally 1.75 mg/kg/h for 12 h before stopping.

#### *3.5.5 Adverse Effects*

Adverse events include sedation, respiratory depression, and cardiovascular events including bradycardia, arrhythmias, and hypotension. Cardiac events have been described in up to 5% of neonates [96, 99, 100], and hence there is a need for close monitoring. It has been suggested that the cardiac effect of lidocaine is less pronounced during hypothermia [93]. A case of methemoglobinemia has recently been described in a newborn [101]. Contraindications include congenital heart disease and treatment with phenytoin.

#### *3.5.6 Summary*

Lidocaine shows promising efficacy as second- or third-line treatment for neonatal seizures, but this has not been confirmed in randomized control trials. It has a narrow therapeutic window requiring cardiac monitoring and adherence to strict dosage regimes.

### 3.6 Bumetanide

Bumetanide is a loop diuretic with well-described pharmacokinetic data and a favorable safety profile in adults and children. It has been used routinely in many neonatal units in the USA for the last 30 years. More recently it has been suggested that it may also be effective in treating neonatal seizure by inhibiting neuronal NKCC co-transporters.

#### *3.6.1 Mode of Action*

$GABA_A$ is a major inhibitory receptor in mature neurons. However, in immature neurons, there is an overexpression of NKCC1 and underexpression of KCC2, which results in a high intracellular chloride concentration, which results in depolarizing $GABA_A$ receptor-mediated action and excitation [102]. Inhibiting NKCC1 would lower the intracellular $Cl^-$ concentration, thus converting GABA activity into an inhibitory process as opposed to an excitatory one. However, recent studies have questioned whether this is a

real phenomenon in vivo [35]. In vitro studies suggest that bumetanide reduces or reverses the depolarizing action of GABA, resulting in reduced neuronal firing in immature neurons [103–105].

#### 3.6.2 Pharmacokinetics

Most available pharmacokinetic data for bumetanide in infants are from critically ill or preterm patients given bumetanide for fluid overload [106, 107]. Elimination follows first order kinetics, and other pharmacokinetic parameters such as volume of distribution, clearance, and half-life are independent of bumetanide dose [106]. Elimination appears to be slower in babies compared to adults. One study suggests that the pharmacokinetic parameters in full-term neonates with HIE are similar to those in published population data [108]. The half-life of bumetanide in critically ill neonates ranges from 1.74 to 7.0 h [109], whereas in neonates with HIE undergoing therapeutic hypothermia, the half-life was slightly longer (8.4 h) [108].

#### 3.6.3 Efficacy

Efficacy data from animal studies look promising for the use of bumetanide in conjunction with phenobarbital. A recent experiment done in rats found that this combination of therapies was significantly more beneficial for hypoxia-induced seizures than phenobarbital alone [110]. In other studies, bumetanide showed more benefit for neonatal seizures than for seizures in postneonatal or early adolescent rats [111].

In a single case report, treatment of a neonate with refractory seizures with a single dose of bumetanide showed some efficacy [112].

So far only one clinical trial has been published [113]: the NEMO trial (Treatment of NEonatal seizures with Medication Off-patent) was an open-label, exploratory dose-finding, pharmacokinetic clinical trial of bumetanide for the treatment of neonatal seizures. Neonates with HIE and seizures not responding to phenobarbital were treated with bumetanide add-on for 2 days. The primary efficacy endpoint was a reduction in electrographic seizure burden of more than 80% without the need for rescue antiepileptic drugs in more than 50% of infants. The trial was terminated early due to adverse events (see below), but evaluation of efficacy data in 14 babies suggested that bumetanide did not reduce seizure burden over and above the second phenobarbital dose. This may be due to limited transfers across the brain–blood barrier [90, 114].

#### 3.6.4 Dosing

No recommended dose exists for bumetanide as an antiseizure agent. The recommended dosing as a diuretic agent ranges from 0.005 to 0.1 mg/kg/day.

#### 3.6.5 Adverse Events

Most trials of bumetanide in newborns indicate that it is well-tolerated and has a good safety profile, even in critically ill or preterm babies. Doses ranging from 0.005 to 0.10 mg/kg were tolerated well by neonates or children younger than 6 months, specifically without incidence of electrolyte abnormalities, hemodynamic change, hypovolemia, or hyperbilirubinemia [107, 109]. In these studies, however, bumetanide was used as a diuretic and thus given to a different population and in a smaller dose than what is proposed for seizures.

In the NEMO study, no short-term, dose-limiting toxic effects were reported, but three of 11 surviving infants had hearing impairment, causing early termination of the trial. Results also highlighted the risks associated with the off-label use of drugs in newborn infants before safety assessment in controlled trials.

#### 3.6.6 Summary

Although preclinical data suggest that bumetanide may have potential as an antiseizure drug for newborns, clinical data so far are not encouraging.

### 3.7 Topiramate

Topiramate has been used for over a decade in children and adults as both add-on therapy [115, 116] and monotherapy [117]. Although it is currently approved for use in children aged 2–16 years, it is used off-label in the neonatal period. Despite only having an oral formulation, its use is gaining support in this population because of its apparent neuroprotective efficacy in animals modeling hypoxic ischemic injury [54, 118, 119].

#### 3.7.1 Mode of Action

Topiramate is a sulfamate-substituted monosaccharide which has multiple mechanisms of action: it enhances GABA activity, inhibits kainate-mediated conductance at glutamate receptors, and modifies $Na^{+}$- and $Ca^{2+}$-dependent action potentials.

#### 3.7.2 Pharmacokinetics

Topiramate exhibits a linear relationship between dose and serum concentration and is not highly protein bound. Approximately 70% of the drug is eliminated unchanged in the urine. Data from children and adolescents aged 1–17 years indicate that infants exhibit higher clearance and shorter half-lives than older children [120, 121]. Pharmacokinetic data for topiramate in babies with HIE are more limited. One small study examined 13 term newborns undergoing hypothermia for HIE [122]. Cooled patients displayed somewhat slowed topiramate absorption and elimination when compared to normothermic babies.

#### 3.7.3 Efficacy

Published data on the effect of topiramate in this neonatal seizures after HIE are scarce. Results from a recent efficacy pilot trial [123] suggests that administration of topiramate in neonates with HIE is safe, but does not demonstrate neuroprotection. However, a trend towards a reduction in epilepsy was observed. Seizures during the neonatal period were not an outcome measure in this study. One small clinical study in newborns with presumed hypoxic ischemic injury and refractory seizures had decreased or no clinical and/or electrographic seizures following treatment with topiramate [124]. However, a randomized controlled trial in infants aged 1 month to 2 years with refractory partial-onset seizures topiramate did not significantly reduce seizure rates [125].

#### 3.7.4 Dosing

There is no approved dosing for neonates. Initial safety data from one small sample indicate that it is safe to use in this population at a dose of 5 mg/kg, and other series indicate 10 mg/kg is tolerated as well among neonates [124, 126]. Doses of 50 mg/kg, however, may be neurotoxic [127].

#### 3.7.5 Adverse Events

As of now, only an oral formulation is available. Topiramate has a good safety profile among neonates and older children [126]. For babies with HIE, doses of 10 mg/kg have caused some irritability, feeding problems with minimal weight loss, and metabolic acidosis [121, 123, 124]. Doses of 5 mg/kg in asphyxiated newborns undergoing hypothermia are tolerated well with no identified adverse events due to topiramate [122, 123]. Topiramate inhibits carbonic anhydrase, causing lowered bicarbonate levels, which can lead to metabolic acidosis. Pediatric patients are more susceptible to this effect of topiramate than adults, although cases of decreased bicarbonate have not been clinically significant [128, 129].

#### 3.7.6 Summary

Topiramate is an emerging therapy for seizures in neonates with HIE, but is currently used off-label. Initial safety data from one small sample indicate it is safe to use in this population at a dose of 5 mg/kg, and other series indicate 10 mg/kg is tolerated as well among neonates [124, 126].

## 4 Neuroprotection and Antiseizure Mediation

Some of the antiseizure medications used in the neonatal period have suspected or proven neuroprotective properties, for example, phenobarbital and topiramate. The evidence has been discussed in the respective paragraphs.

Hypothermia is the current standard for neuroprotection in moderate to severe hypoxic ischemic injury in infants 36 weeks gestation and older. Two types of therapeutic hypothermia are currently used: selective head and whole body cooling. Cooling typically occurs for a duration of 72 h, followed by gradual warming. When hypothermia is initiated within 5.5 h after brain ischemia, it has been shown to be advantageous [130]. Hypothermia is thought to be neuroprotective by inhibiting the cascade of cell injury that culminates in cell death. Evidence from multiple randomized control trials indicates therapeutic hypothermia in neonates with moderate to severe HIE reduces the risk of death or disability at 18–22 months, without significant adverse effects [131, 132]. Animal studies indicate that therapeutic hypothermia can decrease seizures and epileptiform activity in HIE [133, 134]. However, in human studies, the results have been mixed. Some studies conclude that it reduces seizure burden, as measured by cEEG [135]. However, other studies report that electrographic seizures can still be present [1, 136]. Since the introduction of therapeutic hypothermia, the mortality rate has been reduced without an increase in disability rates [132]. Although hypothermia is relatively safe [132], risk factors should be monitored for, including bradycardia, hypotension, renal insufficiency, coagulopathy, electrolyte abnormalities, skin edema, immunological changes, and rebound hyperthermia.

## 5 Conclusions

An ethical dilemma exists regarding the off-label use of medications to manage seizures in newborn babies. As these drugs are not licensed for children this young, we cannot ensure the safety of antiseizure medications to the

same degree as we can in older children and adults. Medications commonly used in older patients have shown adverse effects and poor neurodevelopment in babies. On the other hand, seizures themselves are dangerous and damaging. Thus, there is clearly a need to identify the optimal treatment protocol to manage seizures in this population.

Ideally, novel medications would be developed specifically for asphyxiated newborns. However, if drugs continue to be used off-label for neonates, prospective, randomized controlled trials are needed to clarify precise pharmacokinetics, efficacy, and safety both in the presence and absence of therapeutic hypothermia. In addition, drug interactions of babies receiving polypharmacy are unclear. These studies must diagnose seizures electrographically and employ a large enough sample for powerful data analysis. The existing data are encouraging, but it is difficult to assess efficacy and safety without a control group for comparison, especially considering that a large portion of seizures remit on their own. The use of dried blood spots has been used in some recent drug trials for therapeutic drug monitoring [122]. Their use will improve the ease of studies in the future since the technique is a minimally invasive procedure that requires a small volume of blood from the neonate.

Based on the available literature, phenobarbital remains the standard first-line agent for neonatal seizures, despite its potentially harmful effects and limited efficacy. Possible secondary medications include phenytoin, bumetanide, topiramate, levetiracetam, lidocaine, or benzodiazepines, with no clear indication of which may be most effective. Ongoing trials of these drugs in neonates with or without HIE should provide more direction for clinicians.

**Compliance with Ethical Standards**

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