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The use of phenobarbital and other anti-seizure drugs in newborns

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A B S T R A C T

Neonatal seizures constitute the most frequent presenting neurologic sign encountered in the neonatal intensive care unit. Despite limited efficacy and safety data, phenobarbital continues to be used near-universally as the first-line anti-seizure drug (ASD) in neonates. The choice of second-line ASDs varies by provider and institution, and is still not supported by sufficient scientific evidence. In this review, we discuss the available evidence supporting the efficacy, mechanism of action, potential adverse effects, key pharmacokinetic characteristics such as interaction with therapeutic hypothermia, logistical issues, and rationale for use of neonatal ASDs. We describe the widely used neonatal ASDs, namely phenobarbital, phenytoin, midazolam, and levetiracetam, in addition to potential ASDs, including lidocaine, topiramate, and bumetanide.

1. Introduction

Neonatal seizures affect 1 to 3.5 per 1000 live-born newborns, and their most frequent etiologies are hypoxic–ischemic encephalopathy (HIE), ischemic stroke, and intracranial hemorrhage [1–3]. Management of neonatal seizures varies widely, due in part to the lack of sufficient efficacy and safety data on available ASDs, in addition to evidence suggesting that some ASDs may have deleterious effects on brain development. In fact, no ASD has been approved by the US Food and Drug Administration for use in neonates.

In the absence of strong scientific evidence, most providers use the same ASDs they have used for decades. Some clinicians employ new ASDs in neonates after successful use in older infants and children. In a recent US retrospective report of 9134 neonates with seizures, the use of phenobarbital over the last decade has slightly declined but is still used in 96% of neonates with seizures, largely as a first-line agent. Whereas the use of phenytoin has significantly declined, the use of levetiracetam has increased ten-fold [4].

2. Controversies in the treatment of neonatal seizures

Apart from the controversy regarding ASD choice, which is discussed in more detail below, other controversies persist. The question of whether continuous electroencephalographic (cEEG) monitoring is needed to detect seizures has been settled by numerous studies showing the high incidence of subclinical seizures, and the difficulty of determining whether a clinical event is a seizure [5]. A second controversy concerns the treatment of subclinical (electrographic-only) seizures. Basic science data show that electrographic-only seizures contribute to neonatal brain injury [6,7]. In human newborns, one small study of neonates randomized to receive ASD for EEG-proven seizures showed lower seizure burden and better neurodevelopmental outcome at 18–24 months than among those treated for only clinical seizures [8]. A third controversy is the duration of ASD treatment. For many clinicians, the duration of ASD therapy depends largely on the etiology, but there is no consensus on ASD treatment duration in newborns with acute symptomatic etiologies, whose seizures often subside within days of onset [9].

3. Choice of anti-seizure drugs

Of course, clinicians prefer the most efficacious ASD with the least adverse effects. Unfortunately, currently available data regarding efficacy and safety are inadequate. Studies on neonatal ASD efficacy need to be examined carefully with specific questions in mind regarding the methodology and results. What definition of efficacy was used: cessation of seizures or decreased seizure burden, and, if the latter, what magnitude of seizure reduction? How long was that effect maintained? Was there a control group in

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the study? Was the medication used as first-line therapy or second- and third-line therapies? Seizures from acute symptomatic etiologies typically have a crescendo–decrescendo pattern [10]. Therefore, a medication used late in the course of acute seizures (e.g. as second or third line drug) may be misinterpreted as having good efficacy, when in fact the seizures are subsiding naturally. Another caveat in some of the studies reported in literature is the use of cEEG monitoring. Without cEEG for detection of seizures at baseline, as well as determination of drug response, efficacy cannot be determined with certainty as clinical events might not have been seizures. Moreover, medications may cause electroclinical uncoupling with persistence of the electrographic component without clinical manifestations. To measure efficacy accurately, drugs need to be tested early in the course of seizures, compared with a control group, and their effect monitored by cEEG. Finally, drug efficacy ideally should be associated with improved long-term neurodevelopmental outcome and decreased risk of later epilepsy. Published data on neonatal ASDs should be interpreted cautiously after considering these factors.

4. Effect of hypothermia

Therapeutic hypothermia is standard of care in neonatal HIE, the most frequent cause of neonatal seizures, and needs to be considered with regard to its interaction with ASDs. Data indicate that hypothermia itself is likely to reduce seizure burden [11,12]. In addition, hypothermia may alter ASD pharmacodynamics and pharmacokinetics. Hypothermia mainly affects biotransformation of drugs via reducing the activity of the hepatic cytochrome P450 (CYP450) enzymes, and it can affect enzymatic conjugation. The effect of hypothermia is exaggerated in cases with hypoxic–ischemic (HI)-induced hepatic and renal dysfunction hindering drug metabolism and elimination [13,14]. Similar concerns are evident during rewarming, but in the opposite direction. Rewarming could be associated with increased metabolism and accelerated elimination of drugs leading to significant decrease in drug concentrations [14].

5. Widely used anti-seizure drugs

In this review, we discuss widely used ASDs, namely phenobarbital, phenytoin, midazolam, and levetiracetam, and other potential ASDs for newborns, including lidocaine, topiramate and bumetanide. For each of these medications, we discuss mechanism of action, rationale of use, potential adverse effects, logistical issues, and any interaction with hypothermia. A summary of efficacy, adverse effects, effect of hypothermia and logistical issues is presented in Table 1 [15–46].

5.1. Phenobarbital

Phenobarbital has been used as the standard first-line of therapy for neonatal seizures for decades, and is the drug most frequently used by providers worldwide [4,47–49]. This is likely attributed to available efficacy data, predictable pharmacokinetics with long half-life making it feasible to monitor, and likely most of all, long experience in its use.

Phenobarbital is metabolized by CYP2C19, which may be depressed by therapeutic hypothermia. Although factors affecting renal or hepatic elimination, that may occur in neonatal encephalopathy, could also affect phenobarbital metabolism, the pharmacokinetics of phenobarbital are not generally altered by hypothermia [23,24], so its dosing may not need adjustment for hypothermia.

The most frequently adverse effect of phenobarbital is central nervous system (CNS) depression and potential for respiratory depression requiring additional support. Moreover, there is evidence from multiple animal studies that phenobarbital, as well as other ASDs, induces apoptosis in rodent neurons. This apoptosis involves the cortex, hypothalamus, thalamus, and basal ganglia as well as developing white matter [18–20]. Of note, the average dose of phenobarbital used in these animal studies was 75 mg/kg, which significantly exceeds doses typically used in neonates. In addition, both phenobarbital and phenytoin have been shown to disrupt the synaptic maturation of neonatal rat brain and impair behavior [21]. Long-term effects in rats exposed to similarly very high loading doses of phenobarbital include schizophrenia-like behavioral abnormalities, and impaired learning, memory, and social interaction [22]. It is difficult to determine whether phenobarbital has similar deleterious effects on human neonates at typical doses.

Phenobarbital has been shown to be efficacious, at least partially, in controlling seizures. In a randomized, crossover trial conducted by Painter et al., when 59 neonates with EEG-confirmed neonatal seizures were randomized to receive either phenobarbital or phenytoin, phenobarbital controlled seizures (80% reduction in severity) in 43% of patients, which increased to 57% when both phenobarbital and phenytoin were used in combination [15]. In another small trial using EEG diagnosis of seizures, 50% of patients responded (complete cessation or 80% decrease in burden of seizures) to loading doses of phenobarbital up to 40 mg/kg [16]. In a recent retrospective report, phenobarbital was completely effective in 62.6% and partially effective in 16.5% of neonates to eliminate both clinical and electrographic seizures; this report did not include newborns with status epilepticus [17]. Animal studies suggested that use of phenobarbital during therapeutic hypothermia after HIE insult could be neuroprotective [50]. However, phenobarbital has not been shown to improve neurologic outcome in human studies [51,52]. Additionally, a recent Cochrane review reported insufficient evidence to support use of prophylactic phenobarbital following neonatal encephalopathy [53].

Neonates receiving phenobarbital (or any other ASD) are already at high risk of developmental delay and behavioral impairment because of both the primary hypoxic–ischemic injury and/or the effect of repeated seizures on the developing brain. It remains unknown whether phenobarbital worsens or potentially improves long-term developmental outcome, when effective in controlling neonatal seizures.

5.2. Phenytoin

Traditionally, phenytoin/fosphenytoin has been the most widely used second-line ASD for neonatal seizures, with fosphenytoin preferred over phenytoin due to reduced adverse effects such as local irritation. However, in a recent survey, the use of phenytoin has declined [4]. Adverse effects of phenytoin include arrhythmia, hypotension, and CNS depression [25]. Large doses of phenytoin of 50 mg/kg (far exceeding the typical 20 mg/kg loading dose in humans) was shown to cause similar apoptosis and synaptic disruption in the developing brain of different animal models as did phenobarbital [20,21].

Hypothermia decreases the activities of both CYP2C9 and CYP2C19 that metabolize phenytoin. In children with traumatic brain injury, increased phenytoin concentrations extended beyond the period of therapeutic hypothermia, warranting careful and prolonged monitoring of phenytoin concentrations [26]. Although the pharmacokinetics of phenytoin during neonatal therapeutic hypothermia have not been studied, it is possible that this combination could be associated with prolonged clearance and bradycardia.

Available data show that phenytoin is about as effective as

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