Review Article

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New Treatments for Newborn Seizures

Abstract

The treatments for neonatal seizures, a frequent neurologic emergency, have not altered appreciably in decades. Acute symptomatic seizures and epilepsies with neonatal beginnings are unique from other types of seizures, and advances in diagnostic and pathophysiologic knowledge of these traits give extraordinary opportunities for the development of precision therapeutics with the potential to enhance outcomes. Here, we go over the biology of newborn seizures and a discussion of the research supporting the various treatments that are currently in use. We discuss cutting-edge treatments for the management of acute symptomatic newborn seizures that are now undergoing clinical and preclinical testing. Finally, we explore the function of precision medicines for hereditary neonatal-onset epilepsies and discuss challenges and objectives for creating novel clinical therapies.

Keywords: Neonatal seizures• Pathophysiologic knowledge• Precision therapeutics• Neonatal-onset epilepsies• Novel clinical therapies

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Introduction

The incidence of neonatal seizures ranges from 0.95 to 2.8 per 1000 live births, making them a common emergency. Although the reported incidence of seizures in preterm newborns varies depending on the method of measurement, it is believed to be as high as 5% in population-based and unselected cohorts. Both term and preterm infants can develop neonatal seizures, and the most frequent causes are hypoxic-ischemic encephalopathy, stroke, and cerebral hemorrhage. Neonatal seizures can have less frequent etiologies such infection, electrolyte imbalances (like hypoglycemia or hypocalcemia), and metabolic issues. Therefore, rather than being a symptom of neonatal-onset epilepsy, the majority of neonatal seizures are acute symptomatic seizures. The crucial distinction between acute symptomatic seizures and newborn-onset epilepsy can be used to alter the therapeutic approach to neonatal seizures. This distinction, however, might not be obvious at the beginning of a seizure, and some newborns with epilepsy also have a superimposed acute brain injury. Acute symptomatic seizures normally self-limit during the newborn period after an acquired brain damage, while post-neonatal epilepsy can happen in up to 20% of cases. The possibility of precision therapy will be considered, as neonatal-onset epilepsies are frequently linked to underlying genetic or metabolic disorders. The ineffectiveness of anti-seizure drugs for newborn seizures is a major problem; despite traditional therapies, more than half of neonates continue to have seizures following treatment. The activation of GABA A receptors in adult neurons by the binding of GABA results in an influx of chloride, which induces hyperpolarization of the neuronal membrane and the suppression of action potentials [1]. The activation of the GABA A receptor in developing neurons causes a chloride outflow, which essentially enhances the probability of an action potential firing. The expression of the sodium-potassium-chloride cotransporter-1 (NKCC1), which imports chloride, and the potassium-chloride cotransporter-2 (KCC2), which exports chloride, mediates the reversal of this chloride gradient. Because NKCC1 is expressed more frequently than KCC2 in the developing brain, immature neurons have comparatively high intracellular chloride concentrations. When GABA binds to the post-synaptic receptor, it causes inward calcium currents and the release of the voltage-dependent magnesium block from the N-methyl-D-aspartate (NMDA) receptors, which causes chloride efflux and cell depolarization. Overall, this leads to increased calcium entry and second messenger activation, which raises the risk of seizures and increases brain excitability [2]. The expression of the sodium-potassium-chloride cotransporter 1 (NKCC1), which imports chloride, and the potassium-chloride cotransporter 2 (KCC2), which exports chloride, mediates the reversal of

this chloride gradient. Expression of NKCC1 is more prevalent than KCC2 in the developing brain. The juvenile brain is susceptible to hyperexcitability and seizures as a result of additional developmentally linked expression alterations in excitatory receptors that enable the brain to create suitable activity-dependent developmental processes [3].

Treatment

Phenobarbital: Although there are few randomized controlled trials to back this claim, phenobarbital is strongly advised by the World Health Organization as the first-line treatment for newborn seizures and is the norm at most hospitals. For decades and throughout different geographical areas, phenobarbital has been used fairly consistently for newborn seizures. 97% of neonates treated for seizures got phenobarbital, according to analysis of hospital data from American hospitals from the Pediatric Health Information System, and this practice has remained remarkably constant throughout time. Phenobarbital is also the most often prescribed drug when ant seizure drugs are administered to newborns at hospital discharge. These findings emphasize the significance of phenobarbital in the methods used to treat newborn seizures today [4].

Phenobarbital works by allosterically modulating the GABA A receptor. However, in contrast to the typical inhibitory effect seen in adult models, activation of the GABA A receptor in newborn neurons results in excitement. It is suggested that these developmental abnormalities in newborns account for their lower phenobarbital response rates as compared to older children and adults with epilepsy. Phenobarbital and phenytoin were directly compared in the landmark study by Painter et al. as the first-line treatment for newborn seizure. Phenobarbital may also have a neuroprotective impact, albeit this has not yet been proven. Treatment with phenobarbital (relative to saline placebo) reduced hippocampus cell mortality following a second hit and later life exposure to kainic acid in a rat model of hypoxia-induced seizures. Although the initial response to phenobarbital or seizure burden were not controlled for in this study, there were comparable rates of neuronal cell death between the phenobarbital exposed groups (group 1—hypoxia-induced seizure model exposed to phenobarbital and group 2—uninjured mice with phenobarbital exposure) and the control group of uninjured mice without exposure to the drug [5].

Fosphenytoin and Phenytoin: Up to 15% of individuals with newborn seizures require the administration of fosphenytoin, however this is usually only done when phenobarbital has failed to adequately control the seizures. A phosphorylated prodrug of phenytoin, fosphenytoin has the advantage of having less cardiac toxicity and fewer local extravasation effects than phenytoin, albeit both drugs must be carefully weighed in terms of potential drug interactions. The active metabolite of fosphenytoin, phenytoin, operates to stabilize the neuronal membrane by changing sodium currents. As early investigations of pharmacokinetics were in older children and adults, there was initial concern that parenteral fosphenytoin administration may result in lower serum levels of free phenytoin. However, other research including newborns showed acceptable levels of free phenytoin serum concentration following loading doses of fosphenytoin and comparable conversion times as seen in adult patients. Despite this, enteral administration of phenytoin still presents a difficulty because of variable serum frees phenytoin levels and irregular (often limited) phenytoin absorption [6].

Duration of anti-seizure medication treatment: In order to minimize any potential danger of treatment on the developing neonatal brain, it is crucial to take into account the length of treatment with either existing or novel therapies for neonatal seizures. The majority of neonatal seizures are acute symptomatic seizures, and the peak seizure burden usually occurs during the first 24 hours of commencement. Although most seizures end after a few days, up to 20% may go on to develop post-neonatal epilepsy. Longer antiseizure therapy durations do not seem to diminish the incidence of post-neonatal epilepsy or adverse neurodevelopmental outcomes.

Evident treatment options

Topiramate: The numerous modes of action of topiramate include inhibition of glutamate-receptors, blocking of Na + channels, high-voltage Ca + currents, and isoenzymes of carbonic anhydrase. These qualities have increased the possibility that topiramate will have a neuroprotective effect by reducing excitatory pathways. Both in vitro and in vivo clinical research, including newborn models such periventricular leukomalacia models, have corroborated this. Additionally, there are reports of greater safety in animal models as compared to phenobarbital or benzodiazepines, as well

as the ability to induce neuronal death only at doses much higher than those employed for therapy at the moment. Topiramate for the immediate treatment of seizures in newborns is not well studied. Due in large part to the lack of an intravenous formulation, its use is restricted. Topiramate was utilized less than 1% of the time in a recent comprehensive multi-center evaluation of practice variance in treating neonatal seizures; however, the paper did not state whether topiramate was given for acute symptomatic seizures or neonatal epilepsy [7].

Brivaracetam: A levetiracetam analogue with strong affinity for the Synaptic Vesicle Protein 2A (SV2A), a glycoprotein found in synaptic vesicle membranes, is brivaracetam. In the presence of renal impairment, brivaracetam is well tolerated, has few drug interactions, and can be administered intravenously. Similar to levetiracetam, the specific mechanism of this medication is unknown, and it's possible that each of these medications has a unique effect on the SV2A protein. Although bri- varacetam has been shown to have anti-seizure capabilities in newborn models, animal studies suggest that SV2A may differ in developmental processes due to lower expression. Brivaracetam has been well tolerated in pediatric research with side effects; however there are few clinical data on it during the newborn period [8].

Other agents: The possibility of focusing on certain mechanisms to reduce hyperexcitability is increased by the peculiar physiology of the newborn brain. Since sodium channels and GABA regulation are now the first- and second-line treatments for newborn status epilepticus, respectively, it is necessary to investigate mechanisms other than these in order to treat pharmacoresistant status epilepticus. According to a recent study in neonatal rats, which argued that since neural activity is extremely energy-dependent and necessitates extensive glucose metabolism, it is possible to change metabolism to limit seizures. The researchers wanted to use 2-deoxyglucose (2-DG), a glycolysis inhibitor, to compete with glucose for cell entrance, block glycolysis, and reduce neuronal ATP synthesis. 2-DG was equally efficacious in the rat model of pilocarpine-induced neonatal status epilepticus. Despite the fact that this seems to be an intriguing target for the treatment of refractory sta-tus epilepticus, a lot of work still needs to be done to make sure that these findings apply to more physiological models of hypoxic-ischemic induced refractory seizures and to examine the negative effects of systemic inhibition of glycolysis, even if given for a short period of time. Another recent study suggests that neonatal seizures are significantly influenced by chloride channels, more notably the voltage-dependent CLC-3 Cl- channels [9].

Last but not least, bumepamine, a lipophilic benzylamine derivative of bumetanide, has been investigated for treatment in preclinical models of neonatal seizures. By Nielsen and Feit, bumepamine was initially developed in 1978. Compared to bumetanide, it has 80% less diuretic action and a lower ionization rate at physiological pH. In addition, although the exact mechanism of this effect is not entirely known, bumepamine has demonstrated a more effective dose-dependent impact when compared to bumetanide in potentiating the effect of phenobarbital in animal models of chronic epilepsy. These reasons have generated interest in this substance as a potential therapy for newborn convulsions. Animal model data are the only ones available right now, though [10].

Conclusion

In neonatology and pediatric neurology, the treatment of newborn seizures poses a special challenge because of the distinct pathophysiologic characteristics of the developing brain.

The currently available therapies for acute symptomatic newborn seizures have not altered significantly in decades, despite tremendous breakthroughs in preclinical research. Contrarily, while more than 20 novel anti-seizure drugs have received approval from the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for use in adults, none of them have received approval for use in newborn infants. Introducing novel pharmacological therapies into clinical trials for newborn seizures presents significant obstacles. When safety and efficacy data from adults cannot be sufficiently extended to neonates, there are ethical considerations to be made when weighing the risks and advantages of administering a novel medicine.

Logistical considerations are even more important because volunteers are chosen within hours to days of delivery with the consent of the parents, who have often also experienced a string of concurrently painful medical and emotional experiences. To conduct high-quality trials, it is also required to have good EEG monitoring with real-time interpretation and the capability of performing frequent blood testing. It is

also advised to include a control arm in trials that directly compare second-line treatment choices for seizures that continue despite phenobarbital or current first-line medication (i.e., phenobarbital). Close multidisciplinary cooperation is necessary for these steps.

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