



# Mechanism-Based Treatment for Neonatal Seizures: Still on the Horizon

Epilepsy Currents  
2020, Vol. 20(6S) 53S-55S  
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DOI: 10.1177/1535759720954253  
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**Commentary on: Stafstrom CE.**

**Neonatal Seizures: Is a Novel, Mechanism-Based Treatment Finally on the Horizon? *Epilepsy Curr.* 2006;6:130-132.**

doi:10.1111/j.1535-7511.2006.00121.x

In 2006, when my accompanying commentary was first published, there was considerable optimism that a blocker of the sodium-potassium-chloride cotransporter 1 (NKCC1), such as the loop diuretic bumetanide, would provide the first mechanism-based treatment for neonatal seizures.<sup>1</sup> It made sense, in that bumetanide suppressed seizures in animal models and epileptic activity in brain slices, via the plausible physiological mechanism of shifting the chloride equilibrium potential ( $E_{Cl}$ ) in the negative direction in neonatal neurons.<sup>2,3</sup> By blocking NKCC1 and reducing  $Cl^-$  influx, bumetanide could convert the depolarizing action of gamma-amino butyric acid type A (GABA-A) receptor activation in neonatal neurons into a hyperpolarizing action, as seen in mature neurons. Shortly after the commentary appeared, a proof-of-principle case report was published of an infant with neonatal seizures successfully treated with bumetanide.<sup>4</sup> This experimental and anecdotal clinical evidence led to 2 clinical trials using bumetanide for neonatal seizures in human infants.

One trial was a dose-finding open-label phase 1/2 trial (NCT01434225, called “NEonatal seizures with Medication Off-patent) conducted in 8 European hospitals on neonates with seizures in the setting of hypoxia–ischemia who did not respond to a loading dose of phenobarbital (PHB).<sup>5</sup> The aim of this pharmacokinetic trial was to evaluate the efficacy and safety of 4 doses of bumetanide using a bivariate Bayesian sequential dose-escalation design (each child received active drug, no control group). The primary end point was 80% reduction in electrographic seizure burden in at least half of infants, without use of rescue medications—these comprise very stringent criteria. However, the study was stopped after 14 babies were enrolled, due to documented hearing loss in 3 of 11 survivors. In addition, it was concluded that bumetanide was not affording significant seizure reduction, though more than one-third of infants did not have seizures during the baseline period. When neonates with seizures during the baseline period were

considered separately, bumetanide did appear to reduce the seizure burden,<sup>6</sup> though the benefit was temporary.

The other trial, recently completed, was a randomized, controlled, double-blind dose-escalation study that enrolled 43 newborns (NCT00830531).<sup>7</sup> Its aim was to obtain pharmacokinetic and safety data on bumetanide for electrographic seizures refractory to PHB. The bumetanide was administered early in the course of seizures, and continuous electroencephalography was used before and after treatments to monitor drug response. The findings are currently under review (J. Soul and K. Staley, personal communication, August 3, 2020) and look promising. Seizure burden (minutes/hour of electrographic seizure activity) was used as the outcome measure; compared with the 2-hour baseline recording prior to treatment, there was significant dose- and exposure-related reduction in seizure burden up to 4 hours after bumetanide administration and benefit of all bumetanide doses over PHB monotherapy. Although a larger study would be necessary to establish safety, bumetanide-treated subjects did not experience undue adverse effects (about half had diuresis as expected, and only 2/26 survivors developed hearing impairment). In both studies, hearing impairment assessment is confounded by concurrent gentamicin use and other factors.

Therefore, at this point, the future of bumetanide in neonatal seizure treatment is uncertain, but it may yet find a role as a mechanistically based medication choice. Further safety studies are necessary, and it will be important to understand whether bumetanide or other agents for acute neonatal seizure management provide long-term seizure benefit or even antiepileptogenic effects. Meanwhile, investigators have reported beneficial effects of bumetanide in a number of other disorders characterized by excitation/inhibition imbalance, including autism, schizophrenia, and temporal lobe epilepsy, as summarized in comprehensive recent reviews.<sup>8,9</sup>

Aside from bumetanide, in the past 14 years, no other effective treatment option for neonatal seizures has emerged, but there has been a concerted effort to repurpose levetiracetam



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(LEV) as an alternative to the standard anti-seizure medicines in neonates (PHB; phenytoin; benzodiazepines). Levetiracetam is a broad-spectrum anti-seizure agent that has an uncertain mechanism of action but is presumed to target the synaptic vesicle protein 2A that modulates neurotransmitter release. Reasons for testing LEV were based less on mechanism of action than on practical considerations—LEV is easy to dose and administer and is generally well tolerated in older children, adding to its potential attractiveness in neonates. However, this drug did not fare very well in a recently published trial. A multicenter, randomized, blinded, controlled phase IIb study compared PHB and LEV as first-line agents for neonatal seizures of any cause.<sup>10</sup> The primary outcome measure was seizure freedom for 24 hours. Eighty percent of infants receiving PHB and 28% of infants receiving LEV achieved that outcome, confirming that PHB had better effectiveness. Other treatments are being considered for neonatal seizures, such as topiramate, melatonin, ganaxolone, type 2  $K^+$ - $Cl^-$  cotransporter (KCC2) modulators, and bumetanide analogs.

By 2006, the depolarizing action of GABA and its role in modulating neonatal seizure susceptibility was well recognized. Much had already been learned about the cotransporters that regulate chloride balance and hence excitability of neonatal neurons as well as the extrapolation of chloride transporter function to pathological conditions at postneonatal ages. In the intervening 14 years, even more insight has been gained about the mechanisms of neonatal seizures especially as related to the role of chloride cotransporters.<sup>11,12</sup> Not surprisingly, the chloride transporter story is turning out to be more complicated than originally thought—the idea that the developmental switch of GABA from depolarizing to hyperpolarizing, based on the relative expression of chloride cotransporters over time, is probably oversimplified, for several reasons. First, NKCC1 levels may actually rise until adulthood, rather than peak perinatally and then decline as KCC2 expression increases. Second, these transporters may not be the sole or even primary determinants of intracellular chloride concentration; the distribution and localization of impermeant anions inside and outside the cell may play a critical role in setting  $Cl^-$  homeostasis and thus the direction of the GABA response.<sup>13</sup>

The 2006 commentary also discussed giant depolarizing potentials (GDPs) in neonatal neurons. Giant depolarizing potentials are intrinsically generated potentials, facilitated by GABA, that play a role in rhythmic bursting. An intriguing convergence of the chloride transporter story and the GDP story was the finding that GABA exerts a dynamic role during GDP occurrence.<sup>14</sup> At the beginning of a GDP, depolarizing GABA and glutamate act synergistically to initiate the GDP and depolarize hippocampal CA3 neurons, thereby contributing to neuronal excitation and network synchronization. However, later in the GDP, GABA produces inward  $Cl^-$  current, hyperpolarizing the neuron and constraining its excitation. This dynamic, compensatory physiological situation has fundamental implications for the synchronous firing of neonatal neuronal networks. For example, it would be informative to investigate the role of bumetanide in this

scenario. These experiments represent just one piece of the complex puzzle of the regulation of excitability in neonatal neurons. While no agent has yet been identified that reduces bursting such as GDPs specifically, these findings add a promising dimension that rational options for therapeutics may yet emerge.

My original commentary stated that the hope is that understanding the developmental mechanisms of neonatal seizure generation will lead to improved therapeutics. That hope still exists, of course. The horizon is still there, but remains off in the distance. Lessons learned from both experimental studies and clinical trials will bring the horizon into clearer view.

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