Don't Get BUM'd Out: Bumetanide May yet Prove Beneficial for Neonatal Seizures

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A Pilot Randomized, Controlled, Double-Blind Trial of Bumetanide to Treat Neonatal Seizures

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Objective: In the absence of controlled trials, treatment of neonatal seizures has changed minimally despite poor drug efficacy. We tested bumetanide added to phenobarbital to treat neonatal seizures in the first trial to include a standard-therapy control group. Methods: A randomized, double-blind, dose-escalation design was employed. Neonates with postmenstrual age 33 to 44 weeks at risk of or with seizures were eligible. Subjects with electroencephalography (EEG)-confirmed seizures after ≥20 and <40 mg/kg phenobarbital were randomized to receive additional phenobarbital with either placebo (control) or .1, .2, or .3 mg/kg bumetanide (treatment). Continuous EEG monitoring data from ≥2 hours before to ≥48 hours after study drug administration (SDA) were analyzed for seizures. Results: Subjects were randomized to treatment (n = 27) and control (n = 16) groups. Pharmacokinetics were highly variable among subjects and altered by hypothermia. The only statistically significant adverse event was diuresis in treated subjects (48% vs 13%, P = .02). One treated (4%) and 3 control subjects died (19%, P = .14). Among survivors, 2 of 26 treated subjects (8%) and 0 of 13 control subjects had hearing impairment, as did 1 nonrandomized subject. Total seizure burden varied widely, with much higher seizure burden in treatment vs control groups (median = 3.1 vs 1.2 min/h, P = .006). There was significantly greater reduction in seizure burden 0 to 4 hours and 2 to 4 hours post-SDA (both P < .01) compared with 2-hour baseline in treatment vs control groups with adjustment for seizure burden. Interpretation: Although definitive proof of efficacy awaits an appropriately powered phase 3 trial, this randomized, controlled, multicenter trial demonstrated an additional reduction in seizure burden attributable to bumetanide over phenobarbital without increased serious adverse effects. Future trials of bumetanide and other drugs should include a control group and balance seizure severity. ANN NEUROL 2021; 89:327-340.

Commentary

Seizures are a common manifestation of injury or dysfunction in the neonatal brain and are associated with acute and chronic adverse neurological sequelae. Therefore, finding a safe, effective treatment for neonatal seizures continues to be a high priority.[1] The availability of effective medications is limited by both the inherent physiology of neonatal brain as well as by the lack of adequately powered and designed clinical trials. We find ourselves in a situation not unlike that of several decades ago, with phenobarbital still considered to be the first and best - though not ideal - medicine choice for neonatal seizures.[2]

Bumetanide (BUM) has been touted as a drug with antiseizure effects that might fill the role of a mechanism-based treatment for neonatal seizures.[3] BUM is a loop diuretic, already being used in neonates, that also inhibits the chloride cotransporter NKCC1, present on many cells, including neurons. NKCC1 imports chloride ions (Cl⁻) into neonatal neurons, keeping the intracellular Cl⁻ concentration high. This unique Cl⁻ distribution accounts, at least in part, for the observation that at early stages of brain development (up to early post-term), GABA

(γ-amino-butyric acid) exerts a depolarizing rather than hyperpolarizing effect on many neurons.[4,5] Thus in the developing brain, when GABA-A receptors are activated, Cl⁻ exits the neuron down its concentration gradient, depolarizing the neuron, favoring neuronal hyperexcitability and increased seizure propensity. As an NKCC1 antagonist, BUM has been hypothesized to counteract intracellular Cl⁻ accumulation and thereby reduce cellular excitability. Some animal models attest to the age-related efficacy of BUM against neonatal seizures.[6]

The first multicenter, randomized, double-blind clinical trial of BUM for the treatment of neonatal seizures was published recently.[7] The results of this pilot study have been long awaited for several reasons.

First, the options for effective treatment of neonatal seizures remain extremely limited and the poor efficacy of current treatments has plagued neonatologists and neonatal neurologists for years. The seminal 1999 study by Painter and colleagues,[8] has remained the main source of data with regard to antiseizure medication (ASM) choice for neonatal seizures. In that study, not quite half (~45%) of neonatal seizures were suppressed by phenobarbital or phenytoin; when the first of those drugs didn't

work, addition of the other ASM resulted in seizure control in another 15% of infants. These data indicate that seizures in ~40% of neonates are not controlled, even with dual therapy.

Second, past trials of BUM have yielded disappointing results. For example, in the NEonatal seizure treatment with Medication Off-patent (NEMO) trial, 14 neonates with PHB-resistant seizures received various doses of BUM. The study was terminated when concerns about ototoxicity arose in 3 of 11 surviving patients (all also received aminoglycosides, contributing to potential ototoxicity); though efficacy was not a primary study aim, investigators concluded no significant benefit of BUM for seizure control.[9] However, some authorities have opined that this study was terminated prematurely[10]; more than one-third of infants did not have seizures during the baseline period and when only neonates with seizures were analyzed, BUM did appear to reduce seizure burden.

Third, the possibility that a newer generation ASM with a completely different mechanism of action (eg, levetiracetam, LEV) might be effective for neonatal seizures was put to rest by the recent study of Sharpe et al.[11] This randomized, blinded, multicenter, controlled phase 2b trial compared PHB and LEV for neonatal seizures of any cause. PHB controlled 80% of neonatal seizures whereas LEV benefited only 28%.

The study by Soul et al[7] adds considerable important new information. This randomized, double-blind, multicenter trial was performed on neonates who already had established PHB-resistant electrographic seizures of any etiology. The infants were then randomized to additional PHB plus placebo (control group) vs additional PHB plus various doses of BUM (.1, .2, or .3 mg/kg). This add-on study design allowed comparison of PHB monotherapy (control group) directly with BUM exposure. Continuous electroencephalographic (cEEG) monitoring was used for seizure verification at baseline and during treatment. The investigators enrolled 16 neonates in the PHB plus placebo arm and 27 infants in the PHB plus BUM arm. The primary outcome measure was the pharmacokinetics and safety of BUM as add-on therapy to treat neonatal seizures, while the "exploratory endpoint" was the effect of dose and drug exposure on seizure burden. Seizure burden was defined as the minutes of seizure per hour of cEEG recording. Baseline cEEG was recorded for 2 hours prior to study dose administration, then for an additional 48 or more hours.

Study results are complicated, partly because BUM-randomized patients had a higher baseline seizure burden (by chance), prior to drug administration. On the other hand, this situation might be considered fortuitous, because any beneficial effect of BUM would then be even stronger evidence for its efficacy. Neonates in both arms of the study had similar demographics and side effect profiles, except that BUM-exposed babies had more diuresis, as expected. Though seizure burden was quite variable in both arms, the seizure burden both 0 to 4 hours after BUM exposure and 2 to 4 hours after BUM exposure, was decreased significantly in BUM-exposed babies, and the reduction of seizure burden was dose related. In regard to safety and pharmacokinetic issues, the primary endpoint, there was no excess hearing impairment attributed to BUM (only 2/26 survivors developed hearing loss and both received concurrent aminoglycosides).

It is important to recognize that the notion that neonatal seizures can be ameliorated by blocking the Cl⁻ importing action of NCKK1 has undergone considerable revision and experimental analysis. The relatively simple idea that GABA is depolarizing early in development and later becomes hyperpolarizing, due to the time-dependent expression of the various Cl⁻ co-transporters, is just that–too simple, for many reasons. First, NKCC1 may actually rise until adulthood, rather than peak perinatally and then decline as the expression of the Cl⁻ exporter, KCC2, 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.[12] Third, the expression of NKCC1 is widespread and off-target effects of BUM could be rampant.[13]

The most important results of this pilot study are that PHB plus BUM had a significant benefit over PHB monotherapy for seizure burden reduction in newborns with quite varied seizure etiologies, and without significant adverse effects. Not surprisingly, many questions remain unanswered, requiring studies with a higher number of participants necessary to address these. Future studies will need to balance the severity of group randomization such that a similar seizure burden is present prior to drug exposure. It remains unclear whether BUM can be used as a first-line ASM for neonatal seizures based on the inconclusive (and overall, somewhat underwhelming) human and animal data, but this is unlikely.[14] Seizure responsiveness to BUM (and other agents) may well depend on the seizure etiology, timing of administration, frequency and severity of prior seizures, and many other factors. Nevertheless, there remains theoretical support for BUM as a mechanistically appropriate medication for neonatal seizures. Clearly, there are many other specific physiological features of the neonatal brain that could also be targeted to decrease excitability and thus improve seizure burden. Such efforts are well worth the effort, as neonatal seizures are strongly correlated with future neurologic dysfunction and subsequent epilepsy.

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References

1. Pressler RM, Lagae L. Why we urgently need improved seizure and epilepsy therapies for children and neonates. *Neuropharmacology.* 2020;170:107854.
2. Sankar R, Painter MJ. Neonatal seizures. After all these years we still love what doesn't work. *Neurology.* 2005;64(5):776-777.
3. Stafstrom CE. Mechanism-based treatment for neonatal seizures: Still on the horizon. *Epilepsy Curr.* 2020;20(6S):53S-55S.

4. Dzhala VI, Talos DM, Sdrulla DA, et al. NKCC1 transporter facilitates seizures in the developing brain. *Nat Med*. 2005;11(11): 1205-1213.

5. Staley KJ. Wrong-way chloride transport: is it a treatable cause of some intractable seizures?. *Epilepsy Current*. 2006;6(4):124-127.

6. Dzhala VI, Brumback AC, Staley KJ. Bumetanide enhances phenobarbital efficacy in a neonatal seizure model. *Ann Neurol*. 2008;63(2):222-235.

7. Soul JS, Bergin AM, Stopp C, et al. A pilot randomized, controlled, double-blind trial of bumetanide to treat neonatal seizures. *Ann Neurol*. 2021;89(2):327-340.

8. Painter MJ, Scher MS, Stein AD, et al. Phenobarbital compared with phenytoin for the treatment of neonatal seizures. *N Engl J Med*. 1999;341:485-489.

9. Pressler RM, Boylan GB, Marlow N, et al. Bumetanide for the treatment of seizures in newborn babies with hypoxic ischaemic encephalopathy (NEMO): an open-label, dose finding, and feasibility phase 1/2 trial. *Lancet Neurol*. 2015;14(5):469-477.

10. Thoresen M, Sabir H. Neonatal seizures still lack safe and effective treatment. *Nat Rev Neurol*. 2015;11(6):311-312.

11. Sharpe C, Reiner GE, Davis SL, et al. Levetiracetam versus phenobarbital for neonatal seizures: a randomized controlled trial. *Pediatrics*. 2020;145(6):e20193182.

12. Glykys J, Dzhala V, Egawa K, et al. Local impermeant anions establish the neuronal chloride concentration. *Science*. 2014; 343(6171):670-675.

13. Löscher W, Kaila K. Reply to the commentary by Ben-Ari and Delpire: bumetanide and neonatal seizures: fiction versus reality. *Epilepsia*. 2021;62:941-946.

14. Ben-Ari Y, Delpire E. Phenobarbital, midazolam, bumetanide, and neonatal seizures: the devil is in the details. *Epilepsia*. 2021;62: 935-940.