THERAPEUTIC DILEMMA

Treatment of Seizures in Newborns: The Dilemma of Starting the Right Drug, At the Right Time, in the Right Doses, and Monitoring the Right Endpoints

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CASE

A 25-week gestational age newborn, birthweight 650 grams, has several complications in the first 3 days of life including respiratory distress syndrome treated with surfactant, clinical signs of patent ductus arteriosus which is being evaluated to confirm diagnosis and consideration for ligation, and intraventricular hemorrhage diagnosed on the morning of day 3 of life. On the afternoon of day 3, the patient develops seizure-like activities. Symptoms consist of jerking of the right shoulder followed by chewing motions, and are associated with oxygen desaturation and tachycardia. These symptoms occur about 5 times over a one-hour period. An electroencephalogram (EEG) is ordered and three events are noted during a 30 minute recording. A debate about initiating anticonvulsant therapy ensues; the neurologist wants to wait until the EEG is interpreted to initiate an anticonvulsant, while the pharmacotherapy specialist argues for initiating phenobarbital during the EEG, timed to be given during any observed clinical seizure activity or obvious electrographic seizure activity on the EEG. Based on the neurologist's recommendation, treatment is delayed until the EEG is read and electrographic seizures are confirmed.

Three hours later the neurologist calls to say the EEG indicates presence of electrographic seizures. A recommendation is made to initiate therapy with a 20 mg/kg loading dose of phenobarbital, which would be followed by 15 mg/kg loading dose of phenytoin in the event that phenobarbital failed to control the seizure symptoms. After the seizure activity persists for 3 hours following the phenobarbital dose, phenytoin is started. Clinical symptoms resolve 30 minutes after starting phenytoin, and maintenance doses of both anticonvulsants are started.

ABBREVIATIONS: aEEG, amplitude-integrated electroencephalogram; EEG, electroencephalogram; NICU, Neonatal Intensive Care Unit

On day 3 of therapy, the serum concentration of phenobarbital is 24 mg/L and the total phenytoin serum concentration is 6 mg/L. An EEG on day 4 of therapy shows continued electrographic seizures despite an absence of clinical seizure activity.

Phenobarbital and phenytoin doses are both increased by 20% and drug concentrations and EEG are repeated 3 days later. Phenobarbital and phenytoin concentrations are 26 mg/L and 9 mg/L, respectively. There is no evidence of electrical seizure activity on EEG and the

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neurologist wishes to continue anticonvulsants. The 6–12 months goal for anticonvulsant therapy is to maintain a target concentration of 20 to 30 mg/L of phenobarbital and 8–15 mg/L of phenytoin.

DISCUSSION

Neonatal seizure recognition has become more complicated as our understanding of seizures increases. Since the elegant study by Mizrahi and Kellaway[1] used continuous and simultaneous videographic, polygraphic, and electrographic monitoring, it is apparent that many abnormal seizure-like neonatal movements are not electrical seizures, and many electrical seizures are clinically silent. Thus seizures may be categorized in three ways: 1) electroclinical for those with both a clinical and electrographic presentation of seizures (e.g., clonic, tonic, myoclonic); 2) those with clinical seizure-like activity but absence of concurrent electrographic seizure activity; and 3) electrographic (i.e., those with absence of clinical seizure-like activity but the EEG demonstrates electrographic seizures). This confusing diagnostic situation may result in underestimation of the incidence of neonatal seizures, as over 50% of neonatal electrographic seizures may be undetected.[2]

Electrographic seizures are thought to be harmful to the newborn brain,[3-7] although the damage is different in term and preterm infants. Increasingly, the argument has been that electrical seizures need to be identified. The degree to which electrical seizures need to be suppressed is more contentious. Some authors suggest total control of electrical seizures is unnecessary and only invites drug toxicity.[8,9] Most agree that the ideal goal is total suppression of electrographic seizures to prevent neurologic damage.[4,7,9,10] Whether clinical seizures that have no electrographic seizure activity are harmful in any population is controversial.[11,12]

What about treatment of seizures in patients with electroclinical dissociation? In this situation some seizures occur with, and some without, an associated rhythmic EEG discharge.[13] This phenomenon is thought to occur with subcortical epileptic foci that scalp electrodes may only occasionally detect. It has been well documented when depth electrodes, placed during surgery for epilepsy, reveal seizures in deeper brain structures that scalp electrodes infrequently detect. We cannot rule out the possibility that what appear to be nonepileptic seizures in neonates are actually seizures arising from subcortical structures. At this time, the trend is not to treat seizures that do not have an identified electrical basis.[1,8-10]

In the absence of routine availability of continuous video-EEG monitoring, how should treatment strategies be approached? Many neonatal intensive care units (NICUs) lack the finances and constant availability of a pediatric neurologist to routinely obtain and interpret video-EEG on all high-risk patients. Furthermore, even in centers with video-EEG capacity, some newborns are too unstable to monitor.[7] Alternative approaches are also available. Perhaps the most promising is an amplitude-integrated electroencephalogram (aEEG), also called a cerebral function monitor. Trained neonatologists were able to interpret aEEG and arrive at conclusions that were similar to those of trained neurologists who read a traditional EEG.[14] However, non-expert neonatologists were not as proficient with aEEG interpretation, especially if the seizures were focal, low voltage, or lasted less than one minute.[15] The diagnostic accuracy of intermittent EEG is also only as good as the interpreter. In other venues, neurologists, even those board certified in EEG, have had relatively poor interobserver agreement.[16] Thus the diagnosis of seizures is not easy, even if intermittent EEG is available. Cerebral Function Monitoring is a much less expensive technology than video-EEG and could potentially be mastered by personnel other than a neurologist. Although promising, focal seizures and low voltage seizures outside the range of the electrodes are likely to be missed under any circumstance, and some form of confirmatory EEG is still necessary.

When surveyed about treatment of neonatal seizures, most neonatologists and pediatric neurologists list phenobarbital as the drug of choice, with phenytoin or a benzodiazepine as a common second-line agent.[17,18] The selection of an anticonvulsant is based on habit and experience rather than scientific evidence. The appropriate anticonvulsant for neonatal seizures is increasingly debated.[3,8-10] Clinical

seizures respond to these drugs in about 45% of patients; however, electrographic seizures often persist.[19] This phenomenon, called uncoupling or decoupling, is commonly observed with the use of either phenobarbital or phenytoin.[13,19] In one case series, 58% of 26 patients treated with either phenobarbital or phenytoin had uncoupling.[19] Another case series observed uncoupling in 13 (42%) of 31 neonates with clinical and EEG seizures.[20] This case series described patients treated with phenobarbital, phenytoin, paraldehyde, or diazepam, and suggested that none of these medications were effective in eliminating electrical seizures. Another series of 14 patients with electroclinical seizures who were treated with phenobarbital achieved control of both EEG and clinical seizures in only 29% of patients.[21] Seven of the remaining 10 nonresponders had electroclinical uncoupling. A subsequent report noted that 50% of patients had EEG seizures controlled with phenobarbital 40 mg/kg.[22] The same report showed that when phenobarbital failed as first-line therapy, the likelihood of achieving electrical seizure control by adding a benzodiazepine was very poor. This study raises important questions about whether it is rational to use benzodiazepines as adjunctive therapy to control neonatal seizures. If clinical endpoints are used, a strategy of using phenobarbital doses to achieve serum concentrations up to 40 mg/L resulted in 60% clinical seizure resolution.[23]

The selection of anticonvulsants and their target reference ranges continues to be based on historical experience and studies with major limitations. The argument for targeting phenobarbital serum concentrations of 20 to 40 mg/L, achieved with loading doses of 20 to 40 mg/kg is based on pharmacodynamic studies examining clinical resolution of seizures.[23,24] Some studies examining resolution of EEG seizures also seemed to benefit from loading doses of 40 mg/kg, with an expected concentration of 40 mg/L.[22] Another study comparing phenobarbital and phenytoin suggested targeting free drug concentrations for phenobarbital of 25 mg/L and phenytoin of 3 mg/L.[25] The basis for these targets is not clinical, but rather extrapolation from protein binding studies.[26]

Whether phenobarbital or phenytoin are wise drug choices remains to be determined. Animal and human data support that both phenobarbital and phenytoin impair brain growth and neurodevelopment. Since the brain is rapidly growing during the third trimester and shortly after birth, impairment of brain growth in this critical period is very concerning. Phenobarbital has been shown to impair brain growth in animal studies.[27,28] Human studies also support long-term neurodevelopmental problems following antenatal phenobarbital exposure.[29,30] In one study in which phenobarbital was used *in utero* to prevent intracranial hemorrhage, exposure occurred prior to 34 weeks gestation in the third trimester.[30] Mental Development Index was significantly lower in children than controls. Similarly, phenytoin impairs brain growth and neurodevelopment in rodents with prenatal[31] and postnatal[32-34] exposure. It is useful to note that impaired brain growth occurred at therapeutic concentrations of phenytoin but was less pronounced or absent at lower concentrations. Concerns about neurodevelopmental delays and impaired brain growth following exposure of preterm infants who are technically in their third trimester must also arise in the face of human data showing neurodevelopmental delay after fetal phenytoin exposure.[35] Furthermore, the combination of phenobarbital and phenytoin is associated with smaller occipitofrontal circumference into adulthood and this was associated with persistent learning problems.[36] The cognitive effects of most anticonvulsants have been inadequately studied in children to get a clear sense of their neuropsychologic effects, however, most seem to have some adverse effects in some children.[37]

Numerous other anticonvulsants have been tried with mixed results for success and toxicity. Different anticonvulsants are used by different centers around the world. For example, lidocaine is used in several centers in Europe, but is rarely used in the United States, since this drug also induces seizures when accumulation results in excessive concentrations.[8-10] In patients with refractory seizures, clinicians have been driven to try addition of valproate, clonazepam, midazolam, lorazepam, paraldehyde, carbamazepine, lamotrigine, and a variety of other medications, without regard for subsequent effects of the medications on the developing brain.[8-10] Theoretically, drugs

that would have the greatest efficacy in neonatal seizures would be those that block the NMDA receptor, inhibit presynaptic $GABA_B$ receptors, or act at the voltage-gated channels.[3] This would make phenobarbital less likely to be effective since it enhances postsynaptic GABA inhibition. Some drugs work on Na^+ channels (e.g., carbamazepine or lamotrigine) and are more likely to be effective and may be less toxic than phenobarbital or phenytoin. Unfortunately, both of these drugs are not available in a parenteral dosage form, which is the preferred route to administer to acutely ill patients. Drugs that block NMDA such as topiramate may also be more effective, and animal studies show considerable promise for this drug.[38,39] However, some authors fear that blocking this excitatory amino acid may impair learning and memory in the developing infant.[3] On the other hand, a new rodent study simulating neuronal maturity of a 23–32 week gestation newborn, indicates that topiramate may protect against periventricular leukomalacia following a hypoxic-ischemic insult.[40] This may make topiramate particularly attractive in preterm infants with seizures. Thus we are left with selecting anticonvulsants based on clinical experience and clinician bias until appropriate clinical trials are performed to consider short- and long-term impact of alternative drugs.

So what approach to anticonvulsant therapy is likely to be of greatest benefit to neonates with either clinical or electrical seizures? Assuming that the ultimate goal is to avoid adverse effects on the developing brain, the concurrent impact of the etiology for the seizures as a confounding factor is almost impossible to differentiate. Again, most animal models support that neonatal seizures require immediate attention to avoid subsequent neurologic sequelae.[3-10] The benefits of stopping seizures must be weighed against the toxicity of drugs. It is clear that our current anticonvulsant choices may be toxic to the developing brain and testing of alternative, and potentially less neurotoxic, anticonvulsants is needed. Which endpoint is necessary to decide if adequate therapy is being used? Since electroclinical uncoupling is common with our first-line anticonvulsants, the goal is not only early detection of electrical seizures but suppression of electrical seizure activity in a timely manner. It seems continuous video-EEG, continuous aEEG, or frequent intermittent EEG monitoring is necessary for diagnosis of seizures in neonates at risk, and to confirm response to anticonvulsants during treatment. EEG monitoring appears necessary until electrical seizures resolve. This can not only function as a therapeutic endpoint, but most experts favor stopping anticonvulsants about two weeks after electrical seizures resolve to avoid the long-term toxicities of anticonvulsants. Less than 10% of patients will have a seizure recurrence when anticonvulsants are discontinued prior to discharge if electrical seizures resolved and risk of neurodevelopmental injury is limited.[10,41-43]

It is disconcerting to realize how little we actually know about diagnosis and treatment of neonatal seizures. If undetected or undertreated seizures cause serious neurodevelopmental damage, as seems likely, the consequence of inadequate cerebral function monitoring resources in NICUs is mental and motor retardation, and chronic seizure disorders, occurring in an unnecessarily high percentage of our NICU graduates. It would appear that current drug therapy choices, i.e. phenobarbital and phenytoin, probably add their own neurodevelopmental toxicity, and the wisdom of exposing premature infants to these drugs should certainly be questioned. At this point, there are not many options, since other drugs have even less adequate efficacy and safety data. Certainly the duration of exposure and the serum concentrations of drugs used should be kept to a minimum. Based on the limited continuous video-EEG data in neonates, phenobarbital loading doses of 40 mg/kg (expected to achieve a concentration of about 40 mg/L), should control 50% of EEG-seizures. Until further studies are available, this appears to be the strongest evidence-based approach. Selection of a second anticonvulsant for the 50% not responding would favor the drug with the greatest additional benefit for seizure control. Phenytoin can be expected to resolve EEG-seizures in 27% of patients failing initial phenobarbital.[25] Midazolam failed in all six patients where it was tried as a second-line anticonvulsant.[22] Lidocaine was effective in 3 of 5 patients when it was used as a second-

line anticonvulsant for neonates failing initial phenobarbital therapy.[22] This would seem to favor lidocaine as a potentially worthy drug to study, at least as a second-line anticonvulsant. Topiramate has shown protective effects against hypoxic-ischemic damage, and its value in reducing damage similar to periventricular leukomalacia in preterm animals makes clinical trials in preterm infants as described in our case imperative. Other drugs have yet to be studied under such rigorous monitoring conditions, although this is clearly needed.

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