Editorial

Commentary — Early discontinuation of antiseizure medication in neonatal seizures - Proceed with caution

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1. Introduction

The issue of when to stop antiseizure medication (ASM) in a newborn with acute symptomatic seizures (seizures occurring in the neonatal period and related to an acute brain insult) is of particular importance for two major reasons. Firstly, ASM may be harmful to the brain of the newborn (see later). Secondly, however, seizures per se also may be harmful to the neonatal brain (see later). ASM often has been continued for several months to prevent seizure-related brain injury, including epilepsy, and impaired developmental outcome. In 2011, after detailed study by an international group of experts, a WHO guideline recommended "in neonates with normal neurological examination and/or normal electroencephalography, consider stopping anti-epileptic drugs if seizure-free for > 72 hours" [1]. "Seizure-free" was defined as absence of seizures on continuous EEG.

Stimulated by studies from small and single-center studies supporting the notion that early ASM discontinuation for acute seizures is not harmful [2–4], a prospective, observational, multicenter study at 9 centers of infants with acute symptomatic neonatal seizures, born between July 2015 and March 2018, was carried out [5]. A total of 305 infants, primarily (84%) term born, were studied. The etiologies of the seizures were principally hypoxic-ischemic encephalopathy (43%) and ischemic stroke (26%). In contrast to the WHO recommendations, seizure resolution was defined as only 24 hours free of seizures, and ASM (principally phenobarbital) was discontinued in some even in the setting of abnormal EEG and neurological examination. Among the 270 infants evaluated at 24 months, neurodevelopmental outcome and risk of epilepsy were similar in those in whom ASM was discontinued or maintained at discharge. The authors concluded that their results support "routine discontinuation of ASM after resolution of acute symptomatic neonatal seizures prior to hospital discharge" [5].

The purpose of this commentary is to suggest that the term "routine discontinuation" is too broad and to encourage the neonatologist to evaluate each infant

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individually and, in particular, to consider (1) the neurological disorder causing the seizures, especially the results of brain imaging, (2) the near-discharge neurological examination, and (3) the near-discharge EEG (see later).

2. Deleterious effects of seizures and ASM on the developing brain

Central to the issues of duration of seizure treatment with ASMs are two questions; 1) do seizures cause and/or accentuate neonatal brain injury, i.e., are seizures harmful, and 2) do the interventions to treat neonatal seizures, ASMs, have deleterious effects on the developing brain. Each of these issues is discussed briefly next (for detailed review see [6, 7]).

Experimental and clinical data support the conclusion that recurrent seizures can cause and/or accentuate neonatal brain injury. The newborn infant has a propensity to develop recurrent seizures and neuronal injury in considerable part because of a concentration of excitatory amino acid receptors on neurons of cerebral cortex [8, 9]. When excessively activated, these receptors lead to enhanced Ca^{++} influx, generation of free radicals and cell death. In particular, these receptors have molecular properties that render them more excitable than receptors on mature neurons [10–16]. Moreover, GABA receptors on perinatal neurons are excitatory rather than inhibitory, as in mature brain [6]. This paradox occurs because GABA receptor activation results in Cl^- efflux and depolarization (excitation) rather than the Cl^- influx and hyperpolarization (inhibition) that occur on mature GABAergic neurons. The reason for this phenomenon is that neuronal Cl^- levels are abnormally high in immature cortex because of a developmental imbalance between the two Cl^- transporters that determine neuronal Cl^- levels [6, 17].

Concerning the relation of recurrent neonatal seizures to later epilepsy and impaired neurodevelopment, in animal models of recurrent neonatal seizures, long-term changes in these receptors and transporters can occur and predispose to subsequent spontaneous seizure activity [18–22]. Importantly, these long-term changes could be reversed by targeted therapies. The data support the notion that early post-seizure treatment may mitigate some of the deleterious long-term consequences of neonatal seizures, particularly the later development of epilepsy [6]. In other experimental studies, the principal anatomic correlates of recurrent seizures have included synaptic reorganization of axons and terminals in hippocampus, dendritic spine loss in hippocampus, and impaired hippocampal dentate granule cell neurogenesis [14, 23]. The functional correlates have been deficits in cognition. An additional role of neuronal death secondary to excessive Ca^{++} influx (see earlier) in the genesis of the functional deficits is likely.

Clinical studies have supported the notion that increased neonatal seizures are associated with worse brain injury, later epilepsy and less favorable overall neurological outcome. Studies that have utilized MRI have shown increased neonatal seizure burden to be associated with more severe MRI brain injury [24–28] and worse neurological outcome [24, 26, 28–33]. Nearly all the infants studied had hypoxic-ischemic encephalopathy and were studied both before and after the advent of treatment with hypothermia. The obvious difficulty in such studies is distinguishing whether greater seizure occurrence was a biomarker of more severe injury or an important contribution to brain injury. Studies that have attempted to address this issue suggest that seizures are important contributors [24, 26–28, 31].

Taken together, the data described above suggest that in the human infant, as in experimental models, recurrent seizures in the newborn are deleterious to brain and should be treated sufficiently aggressively to eliminate the seizure activity. Whether the goal should be discontinuation of EEG seizure activity after only 24 hours, as in the study of Glass et al. [5], or for 72 hours, as recommended by the WHO group [1], is not clear. The former interval is recommended by the American Clinical Neurophysiology Society [34].

Concerning deleterious effects of ASMs, the most relevant drug to consider is phenobarbital, since this agent is by far the most widely used ASM. The question of a deleterious effect of phenobarbital on the developing brain was raised by earlier data obtained with rats and cultured neural cells [35–39]. However, the relation of these data to human infants is unclear, largely because the duration of therapy corresponded to a period in the human from approximately the sixth month of gestation to years postnatal. Perhaps more concerning are studies in neonatal rats that showed pronounced apoptotic neurodegeneration within 24 hours after administration of phenobarbital [40, 41]. The neuronal death was associated with reduced expression of neurotrophins and survival-promoting proteins in brain. Recent experimental studies also show disturbances of synaptic

development in striatum [42] and GABAergic maturation in hippocampus [43]. However, some clinical data show that phenobarbital-related reduction in neonatal seizures is associated with more favorable neurological outcomes [6] (see earlier), Moreover, the frequently cited study that chronic use of phenobarbital in infants with febrile seizures results in lower IQ [44] does not appear clearly relevant to the newborn and very young infant, because the children were older and treated for 2 years. Thus, at present, the use of phenobarbital in conventional doses and over relatively short periods has not been proven to be deleterious.

3. Think twice before ASM discontinuation

The optimal duration of ASM therapy for newborns with seizures relates principally to the likelihood of seizure recurrence if the drugs are discontinued. This issue has been discussed in detail elsewhere [6] and is beyond the scope of this commentary. However, three features deserve emphasis here, i.e., (1) the etiology and characteristics of the brain injury causing the seizures, (2) the neurological exam at discharge, and (3) the EEG near discharge.

Concerning the brain injury underlying the neonatal seizures, hypoxic-ischemic encephalopathy and ischemic stroke, the two etiologies that accounted for 70% of all infants with seizures in the study of Glass et al. [5] have different risks for subsequent epilepsy according to the topography of injury. In hypoxic-ischemic encephalopathy treated with hypothermia, recent studies indicate an overall risk of long-term epilepsy to be approximately 15–20% [45–47]. However, risk is increased considerably with involvement of deep nuclear structures (thalamus, basal ganglia) and of watershed regions of cerebral cortex.

In ischemic stroke, the risk of subsequent epilepsy is approximately 20–40% [48, 49]. Factors most predictive of subsequent epilepsy are involvement of the main branch of the middle cerebral artery and especially cerebral cortex within its distribution; involvement of thalamus or of temporal lobe also are predictive of subsequent epilepsy. A reflection of the concern for subsequent epilepsy in infants with stroke in the study of Glass et al. is the fact that 72% of the infants with stroke in the nine Centers were maintained on ASM after discharge [5]. Indeed, only 22 infants with stroke involved in the study had ASM discontinued. This small number renders the

comparative data concerning outcomes in the stroke group seriously underpowered.

The results of the neurological examination at discharge can be useful [6]. In older studies of infants with seizures secondary to HIE, those with normal neurological findings at discharge did not develop subsequent recurrent seizures. However, more data are needed on this issue, especially utilizing a systematic quantitative assessment of the neurological exam. In the study of Glass et al. an abnormal neurological exam at discharge was reported to be no different than a normal exam in prediction of subsequent seizures [5]. However, notably, as with stroke the number of infants with an abnormal neurological examination who had ASM discontinued in the nine Centers was relatively small. Thus, only approximately 20% ($n = 20$) of such infants had ASM discontinued, and thus the conclusion that abnormal neurological examination at discharge should not influence the decision to discontinue is based on the results of a relatively small number of infants.

The results of at least 24 hours of continuous EEG are also of predictive value for subsequent epilepsy. Detailed consideration of this issue is available elsewhere [6, 50–55]. Infants at enhanced risk of subsequent epilepsy include those with burst-suppression pattern or marked overall depression. Some consider the 24-hour seizure-free interval as sufficient to discontinue ASM to be too brief. The WHO recommendation is to consider stopping ASM if the EEG seizure-free interval is 72 hours [1]. Additionally, detailed analysis of outcomes of infants with recurrent runs of sharp waves or spikes that do not reach the 10-second definition of seizure but in whom ASM was discontinued is not available, but such EEG features should give the physician pause concerning discontinuation of phenobarbital.

These three factors should be assessed again on early follow-up. It is beyond the scope of this Commentary to address timing of discontinuation of ASM beyond the neonatal period. In general, reassessment after 1-3 months is appropriate. Prolonged treatment of ASM in infancy should be avoided whenever possible.

The central point is that the neonatologist should consider the totality of the infant's structural and functional neurological status before discontinuing ASM in the neonatal period. The decision to discontinue is not a simple one and should not be characterized as "routine". Nevertheless, the study by Glass et al. is a very important beginning to address this issue. Indeed, their data suggest that many infants

with seizures need not be maintained on ASM beyond the neonatal period. However, as the authors indicate in their conclusion, "larger longer-term studies are needed" [5].

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