Management of seizure activity in the neonatal foal presents a number of challenges. Control of neurological dysfunction and prevention of secondary physical injury is necessary in the first instance. Diagnosis of any underlying medical conditions must occur. Wide-ranging knowledge of the underlying cerebral pathology is essential when formulating a treatment plan. The relatively limited knowledge of and small number of available drugs further complicates both short- and long-term management of seizure activity; however, clinical success is possible with a comprehensive approach to overall patient management. Author’s address: Rood and Riddle Equine Hospital, PO Box 12070, Lexington, Kentucky 40580; e-mail: pmorresey@roodandriddle.com © 2009 AAEP.

1. Introduction
Seizure activity in the neonatal foal can result from cerebral trauma, central nervous system inflammation or infection, compressive intracranial lesions, cerebral edema, congenital epilepsy, or electrolyte disturbances secondary to systemic illness. Because the cause of the seizure activity may not readily be apparent, the first goal of therapy is to control seizure activity and prevent secondary physical injury. Once seizure activity is stabilized, determination of any underlying medical conditions can proceed with an assessment of the systemic health and metabolic state of the neonate.

2. Seizure Recognition
Seizure activity is an indication of forebrain neurological dysfunction as the result of abnormal electrical activity within the brain. Involuntary, spontaneous muscle contractions are accompanied by varying degrees of loss of consciousness. Seizures may be further divided into focal or partial (initially involving a small part of the brain with limited manifestations) or generalized (widespread involvement of the brain with recumbency and loss of consciousness possible). Partial seizures do not necessarily progress into general seizures. Seizures of cerebral origin often remain predictable and non-progressive with respect to their severity and duration. However, when caused by an underlying systemic problem, seizure activity often worsens with any deterioration in the precipitating disease process.

Three phases of a seizure episode are recognized. The pre-ictal period may involve depression, abnormal activity, and star-gazing. The ictal period (overt seizure) encompasses the recognized manifestations of seizure activity: paroxysmal muscle contraction and altered consciousness. The post-ictal phase is one of depression and possible transient loss of neurological function (e.g., central blindness).

Diagnosis of seizure activity in the neonatal foal is challenging but an essential component of successful management of the condition. Only subtle signs suggestive of seizure activity may be displayed. These include any or all of the following: abnormal eye movements, tremors, excessive stretching when recumbent, excessive extensor tone, hyperaesthesia to touch and attempts at physical manipulation, and
apneustic breathing. Overt seizure activity is easier for the clinician to detect: manifestations including rapid nystagmus, paddling, focal, or generalized muscle fasciculations, hyperextension of the limbs and neck, excessive mouth movements (chewing gum fits), and occasionally abnormal vocalization.

Further complicating diagnosis are unobserved episodes of seizure activity. The presence of unexplained physical trauma, for example, nasolabial and gingival excoriation, may be the only evidence of neurological dysfunction (Fig. 1).

3. Pathogenesis of Seizure Activity
Disruption of neural tissue, whether as a result of infection, ischemia, or trauma, involves many processes including vascular and cellular disruption, free radical production, breakdown of cell membrane lipids, and the release of inflammatory mediators. Apoptosis of neurons occurs as a result of aberrant Ca intakes and excitotoxic neurotransmitter release.

Loss of astrocyte functions during cerebral ischemia also affects neuronal cell viability. Astrocytes provide structural, nutritional and metabolic support to neurons. Furthermore, synaptic activity and glutamate uptake are regulated, free radicals are scavenged, and local inflammatory mediator production is modulated.

Excitatory amino acids (including glutamate, aspartate) have been shown to be the final common pathway in many neurologic disorders. Activation of glutamate receptors allows an excessive influx of calcium into neurons through ionic channels. Neuronal swelling results, with the subsequent membrane damage and cell death releasing further glutamate from intracellular storage vesicles, facilitating a self-sustaining cycle of cell damage and aberrant electrical activity.

4. Conditions Associated With Seizure or Seizure-Like Activity
Seizure disorders of the foal can result from compromise of the dam or placenta during the fetal period or from disease processes encountered by the neonatal foal including hypoxic insult and sepsis. Medical management of the foal at risk from the onset of seizure activity should ensure adequate ventilation (avoid hypercapnia that leads to central depression), prevention of hypotension, avoidance of hypoglycemia/hyperglycemia, and control of any detected seizure activity. Underlying medical conditions (infectious, inflammatory, developmental, congenital) must be managed, and any lesions amenable to surgical correction addressed concurrently with seizure control.

Hypoxic Ischemic Encephalopathy and Perinatal Asphyxia Syndrome
The result of cerebral hypoxic or ischemia insult to the neonate, hypoxic ischemic encephalopathy and perinatal asphyxia syndrome (HIE/PAS) is arguably the most common seizure precipitating syndrome faced by the equine clinician. Excitatory amino acids, calcium ions, free radicals, NO, pro-inflammatory cytokines, and products of lipid peroxidation are all thought to contribute to the HIE/PAS syndrome. Compared with the adult, the immature neonatal brain seems to have an increased susceptibility to excitotoxic and free radical damage, with an increased propensity for apoptotic cell death.

The diagnosis of HIE/PAS is dependent on a compatible history and clinical examination findings while ruling out other conditions. Confounding diagnosis, sepsis and major organ dysfunction may occur concurrently. Depressed pulmonary function (decreased ventilation) promotes retention of CO₂, leading to central depression and abnormal acid-base balance. Renal compromise (ischemia) can result in electrolyte (sodium) and fluid balance derangements. With the loss of normal gastrointestinal motility and integrity, intestinal bacterial overgrowth can lead to diarrhea and sepsis.

In the neonatal foal, many recommendations for the treatment of neurological dysfunction resulting from HIE/PAS are empirical and extrapolated from other species.

Trauma
Trauma was the cause of 22% of central nervous system disorders in one equine study. In addition to episodes of seizure activity, trauma can lead to abnormal mentation, gait, and posture. Mild cases often present with subtle neurological deficits, whereas in others, spinal reflexes may be diminished. Severe cases can present in recumbency.

With any case of overt trauma, there may be direct injury of the neural tissue itself. Onset of neu-
rological signs may be delayed because the pathophysiology of central nervous system (CNS) injury is complex and progressive. Ongoing hemorrhage or swelling of neural tissue within the bony confinement of the calvarium, sudden displacement of bony fragments, and disturbances of blood pressure and perfusion exacerbate the initial cerebral insult.

Metabolic Derangement
Glucose levels are frequently abnormal in the compromised neonate, with both hypoglycemia and hyperglycemia potentially having effects on neurological function. Additionally, although other electrolyte disturbances occur, derangements of sodium and calcium are the most relevant with respect to neonatal seizure disorders.

Hypoglycemia
Considering human neonatal glucose concentrations in isolation, insufficient information is currently available to determine a minimum value of glucose occurring during the neonatal period (for any one time or any period of time) below which irreparable hypoglycemic injury to the central nervous system ensues. However, hypoxia, neonatal seizure, and pathological jaundice have been shown to exacerbate hypoglycemic brain injuries in cases of severe and prolonged neonatal hypoglycemia. Hypoglycemia itself has been shown to be a risk factor for perinatal brain injury in term infants who require resuscitation and those that have suffered severe fetal acidemia.

In a recent review, foals with lower mean blood glucose concentrations at admission or high maximum and low minimum blood glucose concentrations within the first 24 h of hospitalization were less likely to survive to discharge. This was thought not to be a result of hypoglycemia causing cerebral dysfunction, but a result of the association of hypoglycemia with sepsis, bacteremia, and the systemic inflammatory response syndrome (SIRS). The effect of hypoglycemia on seizure activity is therefore not proven.

Hyponatremia and Hypernatremia
The brain has limited ability to adapt to alterations in serum osmolality. It is the rapidity with which the sodium disturbance develops that determines if hyponatremia and hypernatremia cause overt neurological deficits. Acute hyponatremia results in cerebral edema caused by the osmotic draw of the hypertonic cell interior. Seizure activity, blindness, and depression can result because of compression of the brain against the bony calvarium. Chronic hyponatremia is less likely to produce neurologic symptoms because osmotic equilibrium has time to occur. The rapid correction of hyponatremia is likely to cause neurological signs because of increased plasma osmolality, causing cell shrinkage by the osmotic draw of water from cells.

By the same osmotic draw, acute hypernatremia may cause shrinkage of brain parenchyma. As with other causes of cerebral injury, neurons produce idiogetic osmoles (osmotically active metabolic byproducts) in an attempt to counter the extracellular hyperosmolality by maintaining intracellular osmotic draw. Unfortunately, these compounds promote intracellular edema during correction of hypernatremia if the rate of correction is not carefully monitored. Parenchymal hemorrhages may occur through tearing of bridging veins, with these sometimes progressing to subdural hematomas in severe cases causing compression of the brain.

Hypocalcemia
Seizure activity (focal or generalized) is the most common central neurologic manifestation of hypocalcemia. Agitation, confusion, and depression may also occur. Tetany is the most frequently recognized peripheral nervous system symptom of hypocalcemia. When the ionized calcium concentration reaches a low enough level, the nerve cell membrane electrical potential reaches a level allowing spontaneous discharge, leading to clusters of irregular, repetitive action potentials. In a case series reported by Beyer et al., five foals with low measured and corrected total serum calcium showed neuromuscular signs including recumbency and seizure-like activity. Corrected total serum calcium levels were <7.5 mg/dl in all the affected foals. Ionized calcium levels for those foals measured were below the normal reference range for the consulting laboratory (<1.58 mM).

Hepatic Compromise
Hepatic dysfunction leads to the systemic accumulation of γ amino butyric acid (GABA) and other undesirable metabolic products such as ammonia. Branched chain amino acids decrease and aromatic amino acids increase. Centrally, these metabolic changes alter the ratio of GABA (inhibitory) and L-glutamate (excitatory) amino acids in favor of seizure propagation. Endogenous benzodiazepine-like compound concentration is increased, leading to centrally mediated depression.

Hyperbilirubinemia
Bilirubin has many toxic intracellular effects. Oxidative phosphorylation is curtailed, membrane structure and function are changed, neurotransmitter metabolism is inhibited, and cell regulatory proteins are altered in structure and function. Prematurity/immaturity, hemolysis, asphyxia, acidosis, sepsis, and increased bilirubin itself may increase bilirubin absorption by nervous tissue. Most important to the neonatal foal is hemolysis, whether by sepsis (intravascular) or neonatal isoerythrolysis (extravascular). Kernicterus, a condition where bilirubin encephalopathy occurs, has been reported in the foal. Degeneration and necrosis of cerebral neurons occurs.
Infectious Agents
Pathogens, whether viral or bacterial, have the ability to cause substantial CNS inflammation by their own actions or by the initiation of an excitotoxic neurotransmitter cascade. Meningitis and encephalomyelitis has been extensively reviewed. The neonatal foal is susceptible to meningitis resulting from systemic bacteremia caused by an increased permeability of the blood–brain barrier.

Developmental or Congenital Cerebral Abnormalities
In one retrospective study, hydrocephalus occurred in 3% of foals that died or were euthanized. Hydrocephalus may be clinically silent or precipitate seizure activity.

Congenital Epilepsy
This condition is reported in some breeds. A recent review of Egyptian Arabians showed seizure activity itself to be self-limiting with age. Complications in affected foals included head trauma and pneumonia.

5. AIDS IN THE DIAGNOSIS OF SEIZURE ACTIVITY

Complete Blood Count and Serum Chemistry
Assessment of the systemic health of any foal displaying seizure activity is essential. A complete blood count (CBC) aids in the diagnosis of systemic infection that may have spread to the CNS. Ongoing cerebral hypoxia as a result of anemia will be suggested. Serum chemistry evaluation assesses major organ system function, chiefly liver (removal of blood borne toxins) and kidney (assessment of electrolyte homeostasis). Immunoglobulin G (IgG) levels are a direct measure of the transfer of passive immunity from the mare, critical for immune defenses in the otherwise hypogammaglobulinemic neonatal foal. A number of studies have shown a relationship between the IgG concentration and the occurrence of neonatal disease including sepsis. Sepsis is a major differential diagnosis in the neonate affected by neurological disease and can itself contribute to neurological dysfunction. Blood gas evaluation assesses pulmonary gas exchange and enables determination of the acid-base status of the foal.

Cerebrospinal Fluid Analysis
In suspected cases of meningitis, cytology and microbiological culture of the cerebrospinal fluid (CSF) is useful for diagnosis, antimicrobial selection, and prognosis. Total protein concentration, nucleated cell count, and red blood cell (RBC) count should be routinely performed. Where increased intracranial pressure is suspected, this procedure should be avoided because aspiration from the atlantal-occipital space can lead to herniation of the brain through the foramen magnum.

Radiography and Magnetic Resonance Imaging
Both radiography and magnetic resonance imaging (MRI) have been reported in the diagnosis of neonatal neurological disease. With radiography, congenital malformations, disruption of bony structures, and deviation of neural tissue by trauma can be visualized. Both plain and contrast studies are possible. MRI is invaluable in the assessment of soft tissue, foci of infection, or vascular disruption.

6. TREATMENT GOALS
Once a diagnosis of a seizure disorder has been made, the treatment plan should seek to address the following clinical goals:

- Manage seizure episodes and any concurrent neurologic dysfunction
- Restore cerebral perfusion and oxygenation if compromised
- Control cerebral edema and inflammation if present
- Provide metabolic requirements of the debilitated patient
- Address concurrent physical injuries and medical conditions if present

With respect to the precipitation of seizure activity within the brain, consideration of a number of therapeutic targets is necessary including glutamate accumulation, aberrant calcium fluxes, free radical formation, lipid peroxidation, and generation of arachidonic acid metabolites.

Blockade of the N-methyl-D-aspartate (NMDA) receptor mediating excitotoxic neuronal damage has been useful in both in vivo and in vitro models of cerebral ischemia and trauma. Cell death results from excessive activation of the NMDA glutamate receptors, allowing excessive Ca influx through a receptor-associated ion channel. Experimental glutamate toxicity can be decreased by NMDA antagonists administered after the initial insult. In addition to NMDA receptor activation, intracellular Ca accumulation may also be caused by calcium-mediated neuronal depolarization and loss of cell membrane integrity. Glutamate excitotoxicity is a cause, result, and potentiator of calcium-induced cellular breakdown; therefore, glutamate control through NMDA receptor blockade provides a rational therapeutic target to ameliorate neuronal damage.

7. READILY AVAILABLE DRUGS USEFUL FOR SEIZURE CONTROL
Although many seizure controlling medications are available in human medicine, veterinary access to most is limited. This review will be limited to those drugs readily accessible to the practicing equine veterinarian.

Benzodiazepines
Drugs of this class are widely used for their anxiolytic, sedative, narcotic, anticonvulsant, and muscle relaxant effects, with differences between members resulting from varying absorption and metabolism. The benzodiazepines are important in the management of seizure disorders associated with
fever and hypoxic insult and are the first choice therapy for status epileptics. Benzodiazepines show high efficacy rates, a rapid onset of action, and have minimal toxicity to the patient.

**Diazepam**

Diazepam is best used in the emergency control of seizures. Chronic oral administration of diazepam is unsuitable for long-term seizure management because efficacy is doubtful. Diazepam has a very short half-life, induces hepatic enzymes, and may create tolerance rendering diazepam ineffective for controlling seizures during emergencies.

The use of diazepam in the control of equine neonatal seizures is widely reported. Rapid onset of short-term control of acute seizures is achieved with minimal depression to the foal. Recurrent seizure activity is often managed with repeated administration of diazepam as required; however, phenobarbital administration to effect is recommended in cases where two or more seizures occur over a short period.

**Midazolam**

Midazolam is the only available water-soluble benzodiazepine. Midazolam is fast acting, rapidly penetrates the blood–brain barrier, and has a relatively short duration of action. Use in the treatment of refractory human neonatal seizures has been reported, with more than one third of all human neonatal seizures being refractory to high dose phenobarbital.

The use of midazolam in the control of neonatal foal seizures has been reported with administration through both the IV and IM route. Initial control of a seizure episode can be readily achieved by bolus intravenous administration, with ongoing seizure control maintained with an intravenous constant rate infusion. Side effects include respiratory depression and hypotension.

**Barbiturates**

**Phenobarbital**

Phenobarbital is used in the management of acute seizure episodes not responding to shorter-acting agents (by IV infusion) and recurrent seizure activity (constant rate infusion, chronic oral dosing). Phenobarbital can be considered a mainstay of seizure control. Onset of action is rapid, with the threshold of neurons to seizure activity initiation and propagation raised. Depression may result on initial administration of the drug; however, in chronic dosage situations, this is overcome by the induction of hepatic enzyme metabolism. Serum levels therefore require monitoring to ensure the foal remains within the therapeutic range during long-term maintenance therapy.

**Pentobarbital**

Pentobarbital is an intravenous anesthetic barbiturate that depresses neuronal excitability by enhancing GABA-coupled responses. Pentobarbital is the first metabolite of thiopental. In comparison to phenobarbital, pentobarbital penetrates the brain faster, allowing more rapid seizure control, and has a shorter half-life, allowing quicker recovery. Sodium pentobarbital is generally reserved for the treatment of uncontrollable status epileptics.

Accumulation may occur with prolonged use because of lipid solubility. Pentobarbital use is associated with respiratory depression, myocardial depression, hypotension, and low cardiac output.

**Phenytoin**

The use of phenytoin in the control of neonatal seizures has been reported. However, little is known about the pharmacokinetics of phenytoin in the equine neonate, with erratic plasma concentrations reported. Considerable depression of some foals has also occurred.

**Cyclohexylamines**

**Ketamine**

The use of ketamine in the management of human refractory status epilepticus has been reported, although this drug has traditionally been avoided in patients with neurological injury. Ketamine has been associated with improved cerebral perfusion, likely by increasing blood pressure because of its sympathomimetic properties. This is in contrast with most medications used for refractory status epileptics that reduce blood pressure.

NMDA receptor antagonism, in addition to being the most important mechanism causing the analgesic effects of ketamine, is also thought responsible for its purported neuroprotective action. Blockade of excitatory transmission at the NMDA receptor provides an approach to the initial treatment of cerebral ischemia. Blockage of excessive NMDA receptor allows regulation of intracellular calcium levels and attenuated induction of NO, reducing neuronal degeneration and death. Cellular morphology was preserved, cellular energy status and ATP production were protected, and reduced cell swelling was noted subsequent to anoxia-hypoxia or excitatory neurotransmitter injury.

Ketamine is useful for the short-term management of seizure activity, being administered as a constant rate infusion after control of a seizure episode. In the author’s experience, this technique is most applicable to those foals maintained in recumbency because of concurrent debilitating medical conditions. The foal is first induced to a light plane of narcosis (diazepam followed by ketamine) and then the infusion is started. Foals vary in their response, some progressing to a state of light but rousable sedation, with others maintaining an appropriate level of awareness and responsiveness to stimulation.
Potassium Bromide

Potassium bromide (KBr) has been used since the 19th century as a human anticonvulsant and sedative. After their first use in 1853, bromides (potassium, sodium, and ammonium) were the mainstay of epilepsy control until replacement by phenobarbital beginning in 1912. It is currently widely used in the management of refractory canine epilepsy. Use in horses has been reported chiefly in adults; however, control in idiopathic epilepsy of foals has been reported. Pharmacokinetics in adult horses have been reviewed. The author has also found KBr useful adjunctively in the control of neonatal seizures incompletely controlled by other agents.

Propofol

Propofol is a short-acting intravenous hypnotic anesthetic agent useful for control of refractory status epilepticus. Propofol may have anticonvulsant activity, because it is GABA-mimetic, stabilizing GABA inhibitory neurotransmitter sites. Use in cases of prolonged seizure activity or status epilepticus has been reported in humans. Use in the neonatal foal for refractory seizure activity is possible with the favorable depressant characteristics of the drug; however, financial considerations may preclude widespread use.

Magnesium

The magnesium ion acts as an antagonist of cell membrane calcium channels in many tissues. It also acts as a voltage-dependent blocker of the NMDA channel, suggesting beneficial effects in the prevention of neuronal cell death and seizure propagation, although this is reduced after neural injury. Cell membrane integrity and permeability have also shown to be improved by Mg administration, as has functioning of the Na+/K+ ATPase membrane pump, which enables a reduction in cell edema.

Gabapentin

Gabapentin is a structural analog of GABA, although the exact mode of action is unknown. It has been reportedly used for neuropathic pain in the horse, and pharmacokinetics have been recently reviewed. Use for seizure control in the horse has not been widely reported. Further study is required before gabapentin can be recommended for seizure control.

8. Supportive Care of Seizure Patients

Treatment of existing trauma, prevention of further injury, strict attention to fluid balance, control of inflammation, and provision of the metabolic requirements of the patient are as integral to successful patient management as control of seizure activity itself.

Wounds, contusions, and decubital ulceration should be aggressively locally managed with topical treatments and dressings. Concurrent systemic antimicrobials to counter bacterial dissemination in the compromised neonate will be required.

Appropriate leg wraps will aid in the prevention of distal limb edema and secondary limb injury. Head protection “bumpers” minimize the occurrence of secondary neurological injury from repeated cranial trauma in the recumbent or seizing foal. If recumbent, the foal should be provided a supportive bed and a means to cleanly eliminate body waste. Slight elevation of the head can prevent dependent edema affecting the brain. Corneal ulceration secondary to abrasion or exposure keratitis can be prevented by regular application of ophthalmic lubricants.

Drug options for sedation of the seizing patient to minimize self-trauma are limited; however, the $\alpha_2$ adrenergic agonists and benzodiazepines possess favorable qualities of sedation and muscle relaxation. Contraindicated drugs include butorphanol (because of a potential increase in CSF pressure) and acepromazine (lowers the seizure threshold).

Fluid Therapy

In addition to meeting the metabolic needs of the patient, appropriate fluid therapy is essential to ensure adequate cerebral perfusion, which may have been compromised by the cerebral insult that precipitated the seizure activity. Restoration of cerebral perfusion allows the re-establishment of autoregulation, the process whereby the brain controls its own perfusion rate and pressure despite fluctuations in arterial blood delivery. The loss of autoregulation has been reported after cerebral ischemia and reperfusion or traumatic brain injury.

An appropriate fluid balance maintains cerebral perfusion and oxygenation while avoiding increased intracranial pressure. Maintenance of appropriate oncotnic pressure with sedation to decrease cerebral energy metabolism is also beneficial.

Systemic dehydration has not been shown to decrease existing cerebral edema, and a negative fluid balance has been proven to be detrimental to overall patient outcome. Overhydration must also be avoided because this potentiates CNS edema after cranial trauma and exacerbates pulmonary edema in recumbent patients.

Although used widely clinically, hypo-osmolar solutions such as 5% dextrose in water increase intracranial pressure caused by decreased serum sodium and increased brain water. Iso-osmolar, polyionic fluids are therefore indicated in the chronic management of neurologically compromised patients once concerns of cerebral edema have been overcome.

Control of Cerebral Edema

Edema of the brain causes compression against its bony confinement and further trauma as well as a decrease in perfusion and oxygenation. Edema...
may be caused by disruption of the blood–brain barrier, cellular disruption causing intracellular water collection, and the result of osmotic imbalances between blood and tissue.\(^5^2\)

The mainstay of edema control has traditionally been the use of diuretics and hyperosmolar agents. Diuretics such as furosemide have little effect on cerebral edema because establishing an osmotic gradient across the blood–brain barrier does not require systemic dehydration.\(^5^3\) Hyperosmolar (osmotic) agents are central to the control of increased intracranial pressure, although firm guidelines for their use do not exist.

**Mannitol**

Mannitol is a polyol (sugar alcohol) used as an osmotic diuretic. As a hyperosmolar agent, mannitol establishes an osmotic gradient across the blood–brain barrier and improves overall blood delivery to the brain while decreasing intracranial pressure.\(^5^4\) Additionally, in common with all hyperosmolar agents, mannitol causes plasma volume expansion with a resultant decrease in blood hematocrit and therefore viscosity, and decreases cerebral blood volume.\(^5^5\)

**Hypertonic Saline**

An intact blood–brain barrier is less permeable to saline than to mannitol; hypertonic saline is therefore a more effective and long-lasting hyperosmolar agent able to resolve cases refractory to mannitol infusion.\(^5^3\) Hypertonic saline solutions decrease brain water and intracranial pressure while temporarily increasing systolic blood pressure and cardiac output.\(^5^1\) The use of hypertonic saline for increased intracranial pressure has been shown to increase survival compared with mannitol use.\(^5^6\) Concentrations used range from 3% to 10%.\(^5^7\)

**Loop Diuretics**

Diuretics such as furosemide will lead to global dehydration of the foal, which is detrimental to outcome because of the decrease in cerebral perfusion and oxygenation resulting from hypovolemia.\(^5^0\) Therefore, in the absence of peripheral or pulmonary edema, loop diuretics are not indicated in seizure cases where cerebral edema is suspected.

**Inflammation**

**Anti-Inflammatories**

Non-steroidal anti-inflammatory drugs (NSAIDs) attenuate inflammation associated with brain and spinal cord injury. Arachidonic acid metabolites promote platelet aggregation and facilitate inflammatory and immune reactions. Experimentally, cyclooxygenase (COX) inhibitors improve cerebral blood flow, decrease edema, protect COX-2–expressing neurons, and attenuate microglial activation.\(^5^8\)

Glucocorticoids are immunosuppressive and diminish monocyte infiltration after cerebral ischemia.\(^5^9\) Glucocorticoids downregulate cytokine-mediated COX-2 expression by monocytes and astrocytes.\(^6^0\) Glucocorticoids inhibit phospholipase A\(_2\), attenuating release of arachidonic acid from the cell membrane and inducible NO synthase (iNOS) expression.\(^6^1\) Upregulation of pro-inflammatory cytokines by nuclear factor \(\kappa\)B (NF-\(\kappa\)B) is also blocked.\(^6^2\)

Cyclooxygenase inhibitors, such as the NSAIDs, should therefore have an additive anti-inflammatory effect if administered concurrently with glucocorticoids. The use of glucocorticoids where cerebral insult is suspected is controversial; however, utility in cases of acute bacterial meningitis has been shown.\(^6^3\)

**Dimethyl Sulfoxide**

Recognized as an anti-inflammatory, dimethyl sulfoxide (DMSO) is also credited as a free radical scavenger, antioxidant, diuretic, vasodilator, and Ca channel blocker. With consideration of the pathophysiology of cerebral insult, DMSO administration is rational in cases of neural trauma.\(^6^4\) DMSO has been shown to rapidly reduce raised intracranial pressure and increases cerebral perfusion without affecting the systemic blood pressure.\(^6^5\)

**Antioxidants**

Lipid peroxidation is considered a major cause of cell damage and death after neurological insult. Antioxidants have been shown capable of inhibiting edema, metabolic derangements, and ischemia of affected tissue.\(^6^6\)

Pretreatment of animals with vitamin E (\(\alpha\)-tocopherol) has been shown beneficial in cases of neurological trauma, decreasing ischemia and enhancing recovery. Vitamin E is thought to act as a peroxyl free radical scavenger. Chronic dosing is necessary because of slow uptake by the CNS tissue, making it an impractical agent for acute treatment.\(^6^7\)

Vitamin C (ascorbic acid) is associated with glutamate release in the brain, suggesting a neuroprotective or neuromodulating effect is possible therapeutically.\(^6^8\) The synaptic action of dopamine is affected, and the NMDA glutamate receptor is altered, which blocks NMDA-gated channel function.\(^6^9\)

**Nutrition**

Protein and energy malnutrition has been shown to exacerbate brain injury and worsen functional outcome during periods of global ischemia. This is as a result of increased oxidative stress and an inflammatory response to ischemia.\(^7^0\) In cases of cerebral trauma, metabolic requirements have been shown to be increased above maintenance levels.\(^7^1\) Provision of adequate nutrition is therefore important in all cases of cerebral dysfunction regardless of the presence of seizure activity. However, seizure activity places extreme demands metabolically on the affected animal, rapidly depleting energy stores.
9. Case Example

A 7-day-old, 45-kg Thoroughbred foal was hospitalized for the recurrence of depression and loss of suckle reflex. The foal had previously been treated beginning at 2 days of age for HIE/PAS, with therapies including antimicrobials, anti-inflammatories, antioxidants (DMSO, vitamin C), and supportive care until the foal could feed itself. The foal was considered to have made a complete recovery after 3 days of treatment.

On admission at 7 days of age, the foal was found to be mildly depressed but in otherwise good condition. Screening blood work did not indicate the presence of infection, major organ dysfunction, or metabolic derangement. Treatment consisted of supportive care, antimicrobial coverage, anti-inflammatory agents, and antioxidants. The foal rapidly improved, with a return to normal behavior and feeding activity within 24 h of admission.

Seizure activity occurred on the third day of hospitalization (10 days of age). Head pressing, tetany, rapid pacing, and dementia were present. Administration of diazepam (5 mg, IV, twice with a 5-min interval) did not resolve the seizures. Phenobarbital was infused (10 mg/kg over 15 min twice with a 20-min interval), which also did not arrest seizure activity. Pentobarbital (3 mg/kg, IV injection) led to a period of narcosis and resolution of the seizure episode. The foal was immediately placed on a ketamine constant rate infusion (induced with 0.05 mg/kg diazepam and 1 mg/kg ketamine, IV, followed by 0.02 mg/kg/min ketamine infusion). After 24 h, the infusion rate was halved and maintained for a further 12 h. During this time, oral phenobarbital maintenance therapy at 4 mg/kg twice daily was instituted. Supportive therapy was discontinued, with the foal becoming ambulatory, and suckling activity was restored. Oral potassium bromide was begun (20 mg/kg three times daily for 2 days, loading dose decreased to 30 mg/kg once daily) in conjunction with the phenobarbital.

The foal was discharged, and no further incidents of seizure activity were reported. Serum phenobarbital levels were measured at 4 days and 3 h after dosage to allow peak concentrations to be measured (8 μg/ml). Phenobarbital and potassium bromide, which were started on the third day of hospitalization, were continued at the same dose in conjunction with the phenobarbital.

Table 1. Drugs Used in Treatment of Neonatal Seizure Disorders

<table>
<thead>
<tr>
<th>Indication</th>
<th>Drug</th>
<th>Dose Rate</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedation</td>
<td>Detomidine</td>
<td>0.005–0.04 mg/kg</td>
<td>IV, IM (high doses). Long-acting.</td>
</tr>
<tr>
<td></td>
<td>Xylazine</td>
<td>0.02–1.1 mg/kg</td>
<td>IV, IM. May exacerbate seizure activity. Short-acting.</td>
</tr>
<tr>
<td>Seizure control</td>
<td>Diazepam</td>
<td>0.05–0.4 mg/kg</td>
<td>IV. Short-acting.</td>
</tr>
<tr>
<td></td>
<td>Midazolam</td>
<td>0.2-mg/kg bolus</td>
<td>IV. Maintain with 0.1–0.2 mg/kg/h constant rate infusion.</td>
</tr>
<tr>
<td></td>
<td>Phenobarbital</td>
<td>5–25 mg/kg</td>
<td>IV loading dose diluted and administered over 15–30 min. Chronic oral maintenance 4–10 mg/kg, q 12 h. Long-acting. Therapeutic levels range 5–30 μg/ml.</td>
</tr>
<tr>
<td></td>
<td>Pentobarbital</td>
<td>3–5 mg/kg</td>
<td>IV. May induce severe respiratory depression.</td>
</tr>
<tr>
<td></td>
<td>Propofol</td>
<td>2-mg/kg induction</td>
<td>IV. Maintain with 1 mg/kg/h constant rate infusion.</td>
</tr>
</tbody>
</table>

Control of inflammation

NSAIDs

- Flunixin: 1.1 mg/kg, IV, q 12 h; PO, q 24 h
- Phenylbutazone: 2.2–4.4 mg/kg, IV or PO, q 12–24 h

Cerebral edema control

- Hypertonic saline: 7 ml/kg, IV as 3% solution
- Mannitol: 1 mg/kg, IV as 20% solution

NMDA blockade

- Magnesium sulfate: 0.05 mg/kg, IV over 30 min. Control excitotoxic glutamate neurotransmitter cascade.
- Ketamine: 0.02 mg/kg/min, IV constant rate infusion. Induces a varying level of central depression with beneficial cardiovascular effects.

Miscellaneous

- Vitamin E: 10–20 IU/kg, PO, q 24 h. Control lipid peroxidation.
- Vitamin C: 100 mg/kg, IV, q 12 h. Antioxidant.
- Thiamine: 10 mg/kg, IV, q 12 h. Metabolic support.
- Dimethyl sulfoxide: 1 g/kg, IV, q 12 h as 10% solution. Free radical scavenger, anti-inflammatory.
- Potassium bromide: 30 mg/kg, PO, q 24 h. Useful adjunct therapy or may be used as the sole agent for long-term management. Therapeutic range 1–3 mg/ml (controversial, adult value extrapolated from other species).
mide were tapered after 1 mo of treatment, being decreased to half dose for a further 2 wk and then discontinued. The foal has continued to develop normally without incident.

The phenobarbital levels measured in this foal are considered to be below the established therapeutic range for horses. Assessment of phenobarbital levels should be performed after the establishment of steady-state concentrations. This occurs after five or six elimination half-lives, with each half-life being 12 hours long. \(^{72}\) In this case, the adjunctive use of potassium bromide may allow a lower level of phenobarbital to maintain effective seizure control.

10. Summary
Control of neonate seizure activity presents diagnostic and therapeutic challenges to the equine clinician. A thorough understanding of the underlying pathology of neurological dysfunction is required. Concurrent or precipitating medical conditions must be managed. Along with management of the seizure activity, re-establishment of appropriate cerebral blood flow, fluid balance, and nutrition is essential to successful management of these cases.

References


