Status Epilepticus

By Aaron M. Cook, Pharm.D., BCPS, BCCCP

DEFINITIONS OF STATUS EPILEPTICUS
Status epilepticus is defined as continuous seizure activity for greater than 5 minutes or consecutive seizures without regaining consciousness over 5 minutes. Status epilepticus is common in the epilepsy population and is often associated with acute, severe neurological injury or illness such as traumatic brain injury (TBI), intracerebral hemorrhage (ICH), meningitis, or pharmacologic toxicity/withdrawal. Overall, the incidence of status epilepticus is about 12 per 100,000 individuals, a value that has increased 50% since the early 2000s (Dham 2014). Status epilepticus is often divided into “convulsive” status epilepticus (in which the patient has obvious clinical manifestations of seizures, mental status impairment, or postictal focal neurological deficits) and “nonconvulsive” status epilepticus (in which the patient has no obvious clinical manifestations of seizure, but seizure activity is revealed on electroencephalogram [EEG]). Refractory status epilepticus is defined as status epilepticus that persists despite treatment with at least two antiepileptic drugs. Outcomes and complications vary greatly among these types of status epilepticus (Treiman 1998).

Epidemiology and Outcomes of Status Epilepticus
Patient outcome is often governed by the response to initial therapy for status epilepticus. Patients with out-of-hospital status epilepticus typically respond well to early initial therapy, with up to 73% of patients having seizure cessation after rapid benzodiazepine administration by emergency medical personnel (Silbergleit 2012). Complications caused by status epilepticus are common, even in patients with clinically evident seizures who receive rapid treatment. Permanent neurological sequelae occur in about 16% of patients who receive early treatment for convulsive status epilepticus, and mortality is 9%–27% within the first 3 months after a status epilepticus event.
(Alldredge 2001, Brophy 2012). Patients with nonconvulsive status epilepticus fare worse, with a mortality rate approaching 65% within 1 month of the epileptic event (Treiman 1998). Patients who lack response to initial conventional status epilepticus therapies and develop refractory status epilepticus also have poor clinical outcomes, with a mortality rate of 34%–60% and over 55% of survivors experiencing neurological sequelae at 3 months (Rossetti 2011, Fernandez 2014).

### AGENTS FOR EMERGENCY THERAPY

Effective initial therapy for status epilepticus is related to several different factors, including pharmacologic agent, adequacy of dose, and timing. Benzodiazepines are the standard of care for emergency treatment of status epilepticus (Table 1-1). In large, prospective, blinded randomized clinical trials comparing different benzodiazepines (and other antiepileptic drugs), intravenous lorazepam has consistently shown efficacy in the early treatment of status epilepticus. In hospitalized patients with status epilepticus, intravenous lorazepam is the drug of choice for initial emergency therapy. In a clinical trial of adults with in-hospital status epilepticus, intravenous lorazepam was superior to intravenous phenytoin (and at least as effective as the other two arms of the study: phenobarbital alone or diazepam plus phenytoin) (Treiman 1998). In out-of-hospital status epilepticus studies, intravenous lorazepam has slightly better response rates (defined as seizure termination) than intravenous diazepam and a response rate similar to intramuscular midazolam (Alldredge 2001, Silbergleit 2012). Midazolam given intramuscularly can rapidly leave the muscle and enter the circulation, where it can exert its pharmacologic effect, producing a time to seizure cessation similar to that with intravenous lorazepam (Hung 1996). The balance of waiting for an intravenous catheter to be placed compared with how quickly an intramuscular injection (by autoinjector) can be given appears to be neutral when comparing intravenous lorazepam and intramuscular midazolam (Silbergleit 2012).

Benzodiazepine therapy must be dosed appropriately and in a timely manner to achieve maximum benefit in patients with status epilepticus. Clinical trials have shown satisfactory cessation of seizure activity with lorazepam doses of 0.1 mg/kg (maximum single dose of 4 mg). In patients weighing more than 40 kg, 10 mg of intramuscular midazolam is also efficacious and beneficial in the prehospital setting or when intravenous access is unavailable. Some clinicians may be wary of using benzodiazepines in a patient with altered mental status without first ensuring control of the patient’s airway; however, evidence suggests a lower rate of intubation in patients who receive benzodiazepines than in those receiving no treatment (Alldredge 2001). This suggests that not treating or poorly treating status epilepticus increases the likelihood of intubation compared with using moderately high boluses of benzodiazepines, further supporting aggressive, prompt treatment of status epilepticus.

### Agents for Urgent Treatment

For patients in whom seizure activity continues despite emergency benzodiazepine therapy, subsequent antiepileptic drugs must be added (Figure 1-1). Fosphenytoin, sodium valproate, and levetiracetam are all viable options for patients requiring further seizure control (Cook 2012). A primary factor for ensuring success with urgent therapy appears to be timing. Whichever agent is selected for urgent therapy, prompt administration of an appropriate dose is more likely to be associated with a positive treatment response. Patients who have delayed therapy (e.g., those who go unrecognized because of nonconvulsive status epilepticus) or inadequate loading doses tend to have a lower response rate to urgent therapy agents (Treiman 1998, Cascino 2001). This underscores that not only is it necessary for clinicians to select the right agent, but timely and adequate dosing is also important for optimal response. Patients who continue to have seizures after emergency therapy should be monitored by continuous EEG, whenever possible, to evaluate for the presence of subclinical or nonconvulsive seizures and response to therapy.

### BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of the pathophysiology of epilepsy and seizure disorders
- General knowledge of the pharmacokinetics and indications for antiepileptic drugs
- General knowledge of therapeutic drug monitoring strategies for antiepileptic drugs
- General knowledge of supportive care in critically ill patients

**Table of common laboratory reference values.**

### ADDITIONAL READINGS

The following free resources have additional background information on this topic:

Table 1-1. Pharmacologic Therapies for Status Epilepticus

<table>
<thead>
<tr>
<th>Emergency Therapies</th>
<th>Loading or Initial Dose</th>
<th>Administration Notes</th>
<th>Potential Adverse Effects</th>
<th>Pertinent Diluents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam</td>
<td>0.15 mg/kg IV (max 10 mg/dose)</td>
<td>5 mg/min IV push</td>
<td>Hypotension CNS depression</td>
<td>Propylene glycol</td>
</tr>
<tr>
<td>Diazepam</td>
<td>5–20 mg rectally</td>
<td>Preferred to intranasal midazolam for infants and small children</td>
<td>CNS depression</td>
<td>None</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>0.1 mg/kg IV (max 4 mg/dose)</td>
<td>2 mg/min IV push</td>
<td>Hypotension CNS depression</td>
<td>Propylene glycol</td>
</tr>
<tr>
<td>Midazolam</td>
<td>0.2 mg/kg intramuscularly (max 10 mg/dose)</td>
<td>Max 5 mg/dose in patients &lt; 40 kg</td>
<td>Hypotension CNS depression</td>
<td>None</td>
</tr>
<tr>
<td>Midazolam</td>
<td>5–10 mg (0.2 mg/kg) intranasally</td>
<td>Must use atomizer adapter with syringe; may not be ideal for infants and small children because of difficult drug delivery</td>
<td>CNS depression</td>
<td>None</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Urgent Therapies</th>
<th>Loading Dose</th>
<th>Administration Notes</th>
<th>Potential Adverse Effects</th>
<th>Diluents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brivaracetam</td>
<td>50–100 mg IV</td>
<td>May infuse over 2–15 min</td>
<td>Dizziness Somnolence Sedation Irritability</td>
<td>None</td>
</tr>
<tr>
<td>Fosphenytoin</td>
<td>20 mg PE/kg IV</td>
<td>Max infusion rate 150 mg PE/min Goal total concentration 10-20 mcg/ml</td>
<td>Arrhythmia CNS depression Hypotension (&lt; phenytoin)</td>
<td>None</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>200–400 mg IV</td>
<td>May infuse over 15–30 min</td>
<td>Bradycardia Dizziness</td>
<td>None</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>1000–3000 mg IV or 30 mg/kg</td>
<td>May infuse over 15–30 min</td>
<td>Irritability, behavioral changes</td>
<td>None</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>20 mg/kg IV</td>
<td>Max infusion rate 100 mg/min Goal concentration 10-40 mcg/ml</td>
<td>Hypotension CNS depression</td>
<td>Propylene glycol</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>20 mg/kg IV</td>
<td>Max infusion rate 50 mg/min Goal total concentration 10-20 mcg/ml</td>
<td>Arrhythmia CNS depression Hypotension Purple glove syndrome</td>
<td>Propylene glycol, ethanol</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Up to 1600 mg (divided two to four times daily)</td>
<td>Oral/enteral administration only</td>
<td>Metabolic acidosis</td>
<td>None, no IV formulation</td>
</tr>
<tr>
<td>Valproate</td>
<td>20–40 mg/kg IV</td>
<td>Max infusion rate 6 mg/kg/min Goal total concentration 50-100 mcg/ml</td>
<td>Hyperammonemia Thrombocytopenia</td>
<td>None</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Refractory Therapies</th>
<th>Dose</th>
<th>Administration Notes</th>
<th>Potential Adverse Effects</th>
<th>Diluents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketamine</td>
<td>1 mg/kg IV push, then 1–10 mg/kg/hr infusion</td>
<td>Should also include sedative infusion to limit dissociative psychosis</td>
<td>Dissociative psychosis Increased ICP? Hypertension</td>
<td>None</td>
</tr>
<tr>
<td>Midazolam</td>
<td>0.2–2 mg/kg/hr IV infusion</td>
<td></td>
<td>CNS depression Hypotension Extended half-life with prolonged use</td>
<td>None</td>
</tr>
</tbody>
</table>
Although many of the options for urgent therapy have clinical data supporting their use, no clinical trials definitively support the use of one antiepileptic drug over another on the basis of efficacy (Brophy 2012). Studies investigating the preferred urgent therapy suggest that the response to any of these options alone is often suboptimal. For instance, patients receiving phenytoin or phenobarbital for in-hospital status epilepticus have less than a 50% overall response rate (i.e., seizure cessation) (Treiman 1998). Other studies suggest the response rate is 70%–88% for patients receiving valproate early in status epilepticus (compared with a 25%–84% response to phenytoin) (Misra 2006, Agarwal 2007). With the lack of consistent benefit, continued research is of utmost importance. A clinical trial is currently under way to compare the use of levetiracetam, fosphenytoin, and valproate for urgent therapy in benzodiazepine-refractory status epilepticus (the ESETT trial) (Kapur 2016). The results of this trial may help practitioners prioritize specific agents in urgent therapy. Before moving on to refractory therapy options that require the patient to be intubated and mechanically ventilated, clinicians should use additional urgent therapy agents if the initial medication chosen fails to abort seizure activity. Despite the lack of a recommendation on the basis of agent efficacy, the characteristics of each agent must be carefully considered from the safety perspective. Traditional urgent therapy options such as phenobarbital and (fos)phenytoin are often avoided because of prolonged infusion times. Phenobarbital is well known to cause hypotension and respiratory depression at intravenous loading and at high infusion rates. Often, endotracheal intubation is needed to protect the patient’s airway.

### Table 1-1. Pharmacologic Therapies for Status Epilepticus (continued)

<table>
<thead>
<tr>
<th>Refractory Therapies</th>
<th>Dose</th>
<th>Administration Notes</th>
<th>Potential Adverse Effects</th>
<th>Diluents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pentobarbital(^b)</td>
<td>10 mg/kg × 1 IV, then 6 mg/kg/hr × 3 hr IV, then 1 mg/kg/hr infusion</td>
<td>1–5 mg/kg/hr infusion range; serum concentration does not typically correlate with burst suppression</td>
<td>CNS depression, Hypotension, Cardiac suppression, Ileus, Extended half-life with prolonged use</td>
<td>Propylene glycol</td>
</tr>
<tr>
<td>Propofol(^b)</td>
<td>20 mcg/kg/min, max 200 mcg/kg/min</td>
<td>High dose (&gt; 80 mcg/kg/min) for prolonged duration (&gt; 48 hr) is associated with PRIS</td>
<td>CNS depression, Hypotension, Hypertriglyceridemia, PRIS</td>
<td>Lipid emulsion (1.1 kcal/mL)</td>
</tr>
</tbody>
</table>

\(^a\)Consider obtaining serum concentration within 2–4 hr of loading dose.

\(^b\)Typically titrated to EEG targets (seizure cessation, burst suppression). IV = intravenous(ly); PE = phenytoin equivalents; PRIS = propofol-related infusion syndrome.

Although many of the options for urgent therapy have clinical data supporting their use, no clinical trials definitively support the use of one antiepileptic drug over another on the basis of efficacy (Brophy 2012). Studies investigating the preferred urgent therapy suggest that the response to any of these options alone is often suboptimal. For instance, patients receiving phenytoin or phenobarbital for in-hospital status epilepticus have less than a 50% overall response rate (i.e., seizure cessation) (Treiman 1998). Other studies suggest the response rate is 70%–88% for patients receiving valproate early in status epilepticus (compared with a 25%–84% response to phenytoin) (Misra 2006, Agarwal 2007). With the lack of consistent benefit, continued research is of utmost importance. A clinical trial is currently under way to compare the use of levetiracetam, fosphenytoin, and valproate for urgent therapy in benzodiazepine-refractory status epilepticus (the ESETT trial) (Kapur 2016). The results of this trial may help practitioners prioritize specific agents in urgent therapy. Before moving on to refractory therapy options that require the patient to be intubated and mechanically ventilated, clinicians should use additional urgent therapy agents if the initial medication chosen fails to abort seizure activity. Despite the lack of a recommendation on the basis of agent efficacy, the characteristics of each agent must be carefully considered from the safety perspective. Traditional urgent therapy options such as phenobarbital and (fos)phenytoin are often avoided because of prolonged infusion times. Phenobarbital is well known to cause hypotension and respiratory depression at intravenous loading and at high infusion rates. Often, endotracheal intubation is needed to protect the patient’s airway.

### Figure 1-1. Proposed algorithm for treating status epilepticus according to available evidence. Lorazepam is the drug of choice for initial therapy, followed by an antiepileptic drug such as phenytoin, valproate, or levetiracetam. Additional therapies may depend on the patient’s need for intubation and other patient-specific factors.
and prevent apnea. Intravenous phenytoin is traditionally associated with hypotension and arrhythmia with rapid infusion. Recommendations suggest limiting phenytoin infusions to 50 mg/minute or less; however, starting at a much lower infusion rate, such as 10 mg/minute, and titrating according to hemodynamic response is prudent. Phenytoin also contains propylene glycol, as do other antiepileptic drugs, including phenobarbital and lorazepam, and caution should be exercised when using these drugs concomitantly to avoid propylene glycol toxicity. Propylene glycol is a vesicant, and accumulation may lead to a severe hyperosmolar anion gap metabolic acidosis (Miller 2008). Fosphenytoin may be given more rapidly than intravenous phenytoin (no more than 150 mg/minute), but this rate is still limited by potential cardiovascular adverse events and the time to conversion to active drug in vivo. Other antiepileptic drugs such as valproate, levetiracetam, and lacosamide may be given more rapidly, often in as few as 5 minutes. Quicker infusions have many practical advantages, including reduced duration of intensive monitoring for infusion-related adverse effects, reduced time from ordering to start of infusion, and quicker achievement of therapeutic concentrations, though this has not yet been proven to affect efficacy.

The pathophysiology of status epilepticus suggests that rapid seizure cessation mitigates neurological and metabolic complications. Prolonged status epilepticus may compromise the effectiveness of traditional treatments and place the patient at risk of refractory status epilepticus (Figure 1-2). In animal models of prolonged status epilepticus, benzodiazepine receptors undergo endocytosis after about 30 minutes of status epilepticus, leading to a benzodiazepine-refractory state (Chen 2006). A concomitant increase in N-methyl-D-aspartate (NMDA)-glutamate receptor expression leads to an excitatory state in the brain that perpetuates status epilepticus and increases cerebral metabolic needs. In patients with refractory status epilepticus, the response rate to the typical antiepileptic drugs used for urgent therapy is typically less than 20% (Treiman 1998, Claassen 2002).

Agents for Refractory Treatment

Traditional treatment of refractory status epilepticus consists of inducing a pharmacologic coma with the goal of achieving an isoelectric EEG (i.e., burst suppression), halting electrographic seizure activity. Several agents have been used in this situation, including midazolam, propofol, and pentobarbital. Although little prospective research has compared these options directly, a meta-analysis has summarized the safety and efficacy of these agents in refractory status epilepticus (Claassen 2002). The previously evaluated agents were comparable with respect to overall outcome (background suppression on EEG), though pentobarbital was associated with fewer breakthrough seizures than midazolam and propofol. More recently, reports on the use of a high-dose midazolam infusion (mean dose 0.3–0.4 mg/kg/hour) suggest that this increased dose has efficacy similar to pentobarbital with a reduced incidence of hypotension (Fernandez 2014).

Anesthetic-level doses of these agents are typically necessary to achieve burst suppression. This is problematic because these agents are associated with significant hypotension at the required dosage (Claassen 2002). Perhaps the most harmful of the three options is pentobarbital, which is not only a direct vasodilator but also an inducer of myocardial depression with prolonged use and high doses (Cook

**Figure 1-2.** Receptor changes in prolonged status epilepticus. Under normal conditions (left), neurons have homeostasis with respect to excitatory (blue circles = glutamate, blue receptors = NMDA) and inhibitory (red circles = GABA, red receptors = GABA) stimuli. After prolonged status epilepticus (right), NMDA receptors up-regulate on the postsynaptic surface, causing increased excitation. Concomitantly, GABA receptors also undergo endocytosis, further perpetuating the excitatory imbalance.

GABA = γ-aminobutyric acid; NMDA = N-methyl-D-aspartate.
High-dose propofol infusions (for as few as 48 hours) have been associated with propofol-related infusion syndrome, which can quickly lead to cardiovascular collapse and death if not recognized early in the process of this dangerous adverse effect (Vasile 2003). Midazolam infusions are less commonly associated with hypotension than pentobarbital or propofol. Consideration of the differences in formulations among these agents (particularly the diluents present in pentobarbital and propofol) may factor into selecting the optimal agent for individual patients, especially those receiving high-dose therapy.

High doses of these lipophilic sedatives can also lead to drug accumulation and prolongation of the context-sensitive half-life of these agents. Midazolam has a pharmacologically active metabolite (1-hydroxy-midazolam) that may be prolonged in the critically ill population or in those concomitantly receiving CYP inhibitors (Power 1998). The secondary glucuronide metabolite is less active but may accumulate in patients with renal dysfunction (Bauer 1995). Prolonged deep sedation and drug accumulation are harmful to ICU patients, in general, and further complicate matters in patients with refractory status epilepticus, in whom clinicians wish to evaluate potential deficits in neurological function as the pharmacologically induced coma subsides.

Titrating these agents to burst suppression and halting electrographic seizure activity are acceptable goals of therapy because data showing the superiority of one end point over another are lacking. Practically, if adding an anesthetic infusion leads to seizure cessation, this would seem to be the optimal goal and would likely lead to less drug exposure. However, in some patients, seizure control does not occur without achieving an isoelectric EEG (i.e., burst suppression), which obliterates cortical electrical activity and presumably halts the seizure process. When burst suppression cannot be achieved despite high doses of one agent or if unacceptable adverse events occur, transitioning to another therapeutic option may be necessary. Of note, inducing a pharmacologic coma is associated with a very high mortality rate in said patients (about 60%) (Claassen 2002). These observed poor outcomes may reflect selection bias because this strategy is reserved for the patients with the most refractory disease. Complications specifically from inducing a pharmacologic coma may also contribute significantly to poor outcomes in refractory status epilepticus, though observational data appear to suggest this is not likely a factor (Alvarez 2016). More research is needed on the precise role of burst suppression therapy in refractory status epilepticus, particularly with respect to the optimal timing of initiation and impact on neurological outcome.

Intravenous ketamine is an emerging alternative option for pharmacologic coma in patients with refractory status epilepticus. Ketamine does not have traditional antiepileptic mechanisms of action in most seizure models and will not achieve burst suppression, even at high doses. However, given the role of NMDA and glutamate in the pathophysiology of refractory status epilepticus, antagonizing NMDA receptors with ketamine is an attractive and logical option. Several case series and case reports support ketamine use in refractory status epilepticus, though the dosage used, timing of initiation, and therapy duration vary considerably (Sheth 1998, Synowiec 2013). The concern for intracranial pressure elevations associated with ketamine has waned in recent years, though care should be taken in patients with disturbed cerebral autoregulation and those who have a more intense cardiovascular response to ketamine (Zeiler 2014, Zeiler 2014). Ketamine, especially at high doses, is commonly combined with other sedating agents (e.g., midazolam or propofol) to reduce the incidence or severity of the dissociative psychosis that may occur.

Progesterone derivatives (also known as neurosteroids) have been investigated as potential therapeutic options in patients with chronic or refractory seizures. Perimenstrual seizure exacerbations clearly fluctuate depending on progesterone concentrations, suggesting neurosteroids have antiepileptic actions (Herzog 2015). The mechanism of neurosteroid antiepileptic activity appears to be related to interaction with γ-aminobutyric acid (GABA) receptors in the brain, where they may augment GABA-minergic activity (Belelli 2005). High neurosteroid concentrations also result in direct GABA activation. Data analyses from a refractory status epilepticus model suggest that delayed treatment of seizures affects benzodiazepine response but that the response to the neurosteroid allopregnanolone is preserved (Rogawski 2013). A clinical trial is evaluating allopregnanolone use in patients with super-refractory status epilepticus (status epilepticus lasting more than 24 hours) (Ferlisi 2012). Neurosteroids appear to be very well tolerated, unlike many of the current therapies for refractory status epilepticus, with clinical trials of oral allopregnanolone analogs reporting a low incidence and mild severity of adverse events.

Additional strategies may be considered in super-refractory status epilepticus, particularly when pharmacologic coma fails. Limited evidence supports the use of inhaled anesthetics, lidocaine infusion, electroconvulsive therapy, ketogenic diet, or surgical intervention in patients with status epilepticus, but positive case reports and case series have been published (Brophy 2012, Ferlisi 2012). One large prospective study investigating the role of hypothermia (32–34°C for 24 hours) in patients with refractory status epilepticus showed that hypothermia did not improve 90-day neurological outcomes and resulted in more adverse events (Legriel 2017).

**COMMON CAUSES OF STATUS EPILEPTICUS**

The etiology of status epilepticus should be thoroughly investigated because it has implications for the agent selected for initial treatment. Almost 50% of patients presenting with...
status epilepticus have a history of epilepsy, and in many cases, the acute seizure may be the result of medication non-adherence or planned tapering of antiepileptic therapy (Cook 2012). In this setting, reinitiating the prescribed antiepileptic or escalating the tapered medication may be prudent. For example, patients who previously had seizure control but then were nonadherent to, or were tapering, phenytoin and who present with a subtherapeutic serum concentration should be loaded on phenytoin rather than initiated on a different urgent therapy option. Reasons for nonadherence should also be considered when developing the antiepileptic regimen for these patients once seizure control is achieved. Status epilepticus may also be an exacerbation of a patient’s seizure disorder. In these cases, using benzodiazepines for emergency therapy is appropriate to abort the seizure, with subsequent therapy targeting optimization of the home antiepileptic drug regimen.

Patients who present with status epilepticus secondary to a structural neurological event such as a TBI or an ICH may require a different approach. In these patients, seizure prophylaxis as well as urgent therapy strategies must be considered. Phenytoin is the primary agent recommended for prevention of early seizures (within the first 7 days) after TBI. (Carney 2016) Levetiracetam is increasingly utilized in clinical practice, despite low quality clinical data supporting its use to this point. (Jones 2008, Zafar 2012, Szaflarski 2015) The use of valproate in patients with a TBI is often avoided because data analyses suggest a trend toward increased mortality in the patients receiving valproate for seizure prophylaxis (Temkin 1999). Valproate use in the context of status epilepticus and trauma is not as well defined, but because of the possibility of increased mortality in this population, an alternative antiepileptic is advisable for urgent therapy.

In patients with a nontraumatic intracranial hemorrhage, seizure prophylaxis is not recommended. Nevertheless, the risk of seizures in this population is high, observed in up to 30% of those presenting with coma secondary to an ICH (Vespa 2003, Claassen 2007). Phenytoin is the most-studied agent for both prophylaxis and treatment of seizures in those with an ICH. However, patients with an ICH or a subarachnoid hemorrhage may have reduced cognitive recovery

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**Patient Care Scenario**

A 54-year-old woman (height 62 inches, weight 60 kg) is admitted after a craniotomy for a temporal glioblastoma multiforme (GBM). She has been taking temozolomide oral therapy for her GBM. In the recovery unit, she has focal seizure activity for about 5–10 minutes, for which she is given lorazepam 2 mg intravenously once and a loading dose of fosphenytoin 1200 mg phenytoin equivalents intravenously. Her Glasgow Coma Score remains abnormal compared with preoperation (E4-M5-V3), and her head CT reveals only postoperative changes and no hematoma. Her current medications include dexamethasone 4 mg intravenously four times daily, famotidine 20 mg intravenously twice daily, metoprolol 25 mg orally twice daily, and temozolomide 200 mg/m² orally daily (currently held during the inpatient stay). Preoperative laboratory values were as follows: Na 145 mEq/L, K 4.1 mEq/L, SCr 0.98 mg/dL, glucose 145 mg/dL, magnesium 2.0 mg/dL, and albumin 2.3 g/dL. The neurosurgeon orders an EEG and is concerned that she continues to have seizures. What would be best to recommend for this patient’s antiepileptic therapy?

A. Continue phenytoin  
B. Valproate  
C. Phenobarbital  
D. Levetiracetam

**ANSWER**

The patient clearly needs continued antiepileptic therapy. However, continuing phenytoin may not be the best option in this scenario. The patient received an adequate loading dose without obvious therapeutic benefit. In addition, prolonged phenytoin continuation will induce dexamethasone and temozolomide metabolism, which may complicate GBM therapy in the future (reducing dexamethasone efficacy and increasing active metabolites of temozolomide, respectively). Safe and accurate phenytoin dosing will be complicated by concomitant dexamethasone and hypoalbuminemia. No obvious electrolyte issues need to be acutely addressed. Potential options supported by the literature and current guidelines include valproic acid, levetiracetam, midazolam infusion, and phenobarbital. Valproic acid may be a viable selection in this case, though it will increase the free fraction of phenytoin acutely. Valproic acid may also contribute to the bone marrow suppression adverse events common with temozolomide. Midazolam and phenobarbital may cause respiratory depression acutely, which may increase the need for endotracheal intubation. Ideally, the decision to intubate a patient with status epilepticus is made to protect the airway because of prolonged seizures, rather than because of the adverse effects of status epilepticus therapy. In this case, levetiracetam may be considered the optimal second option for antiepileptic therapy because of its relative lack of drug-drug or drug-disease interactions and modest support from the most recent guidelines for urgent status epilepticus therapy. A levetiracetam loading dose of around 30 mg/kg intravenously (or 2 g in this patient) would be appropriate. Continued treatment with intermittent boluses of lorazepam should also be considered.

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when receiving phenytoin (Naidech 2005). Conversely, levetiracetam was associated with improved cognitive outcomes in a small cohort study, which may lead practitioners to select this agent over other options for patients with an intracranial hemorrhage in whom seizures need to be managed (Taylor 2011).

**Technologic Considerations**

Toxicological etiologies for status epilepticus present specific challenges related to selecting antiepileptic drugs. Chronic exposure to benzodiazepines and ethanol is hypothesized to induce changes in receptor density and characteristics within the CNS, most notably reductions in GABA receptor concentrations and desensitization of those receptors still present on the surface of the neuron. In addition, NMDA receptors may become sensitized and potentially shuttled to the cell surface in increased numbers in an attempt to maintain a homeostatic resting membrane potential within the neuron. Withdrawal from benzodiazepines or ethanol, after chronic use, leads to an underactivity of GABA function and a surge in excitatory stimulus because of the up-regulation and sensitization of NMDA receptors. These changes lead to excessive excitatory activity and propagation of seizure (Ashton 2005).

For treatment of seizure caused by withdrawal from either benzodiazepines or ethanol, benzodiazepines are preferred. Other situations such as hypoglycemia (intravenous dextrose) or isoniazid-induced seizures (high-dose intravenous pyridoxine) have specific antidotes (Table 1-2).

The potential for adverse effects to become additive should be considered when selecting agents for urgent therapy. For example, patients with status epilepticus may present with a history of a cardiac arrhythmia or a syndrome commonly associated with a cardiac arrhythmia (e.g., tricyclic antidepressant overdose). Clinicians should be wary of using phenytoin in these situations because of the additive potential for generating arrhythmias. Likewise, for acute acetaminophen overdoses with progressive hepatic dysfunction, antiepileptic drugs that are not hepatically metabolized are preferred. Renally eliminated agents such as levetiracetam or, to a lesser extent, lacosamide may be viable options in these patients.

**TIMING**

The time to treatment of patients with status epilepticus likely largely affects the treatment response. Rapid treatment is imperative in status epilepticus, particularly in the emergency phase, because of the time course of pathophysiological changes typical in refractory status epilepticus (Figure 1-2). Animal data analyses of pretreatment or immediate treatment for induced status epilepticus clearly show the benefit of prompt cessation of seizures (Chen 2006). In a landmark study, patients who were randomized to receive a benzodiazepine during transport to the hospital in out-of-hospital status epilepticus were 2–4 times more likely to have status epilepticus terminated on admission than were those not receiving therapy (Alldredge 2001). This clearly shows that early, appropriate therapy is beneficial. Patients with delayed treatment, as often seen with nonconvulsive status epilepticus, have a significantly reduced response to initial therapy (Treiman 1998). Choosing the correct agent and giving it promptly are likely not the only important factors governing response. Suboptimal phenytoin loading has resulted in a lower response rate than adequate dosing (Cascino 2001). This suggests that the right drug at the right time at the right dose is needed to optimize response in status epilepticus. Overall, there appears to be about a 30-minute therapeutic time window for treatment of status epilepticus to reduce the likelihood of status epilepticus becoming a more treatment-refractory condition.

**Drug-Drug Interactions and Pharmacokinetic Considerations**

The current evidence-based guidelines for the treatment of status epilepticus do not suggest preferred agents, nor do they recommend which agents should and should not be used together. In contrast to areas such as infectious disease

<table>
<thead>
<tr>
<th>Specific Indication</th>
<th>Medication</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premorbid isoniazid therapy</td>
<td>Pyridoxine</td>
<td>1 g for every 1 g of isoniazid consumed, if overdose 5 g × 1 for empiric treatment (infused IV 0.5 g/min)</td>
</tr>
<tr>
<td>Hypomagnesemia, glomerulonephritis, hypothyroidism, eclampsia</td>
<td>Magnesium</td>
<td>1–4 g infused over 1 hr</td>
</tr>
<tr>
<td>Wernicke encephalopathy, history of chronic alcohol ingestion</td>
<td>Thiamine</td>
<td>500 mg IV infused over 1 hr</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Dextrose</td>
<td>25–50 mL of 50% dextrose in water IV infused over 5–10 min</td>
</tr>
</tbody>
</table>
### Table 1-3. Select Significant Drug-Drug Interactions with Agents Used for Status Epilepticus

<table>
<thead>
<tr>
<th>Induction of Hepatic Metabolism (Inducing agent inducer ↔ Drug with reduced exposure)</th>
<th>Inhibition of Hepatic Metabolism (Inhibiting agent ↔ Drug with increased exposure)</th>
<th>Clinical Impact (additive effects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenobarbital ↔ Azole antifungals</td>
<td>Clobazam ↔ Phenytoin</td>
<td>Lacosamide ↔ β-Blockers (increased risk of PR interval/bradycardia)</td>
</tr>
<tr>
<td>Phenobarbital ↔ Carbamazepine</td>
<td>Conivaptan ↔ Midazolam</td>
<td>Lacosamide ↔ Calcium-channel blockers (increased risk of PR interval/bradycardia)</td>
</tr>
<tr>
<td>Phenobarbital ↔ Dexamethasone/corticosteroids</td>
<td>Erythromycin/clarithromycin ↔ Midazolam</td>
<td>Phenytoin ↔ Acetaminophen (increased risk of acetaminophen toxicity)</td>
</tr>
<tr>
<td>Phenobarbital ↔ Erythromycin/clarithromycin</td>
<td>Eslicarbazepine ↔ Phenytoin</td>
<td>Phenytoin ↔ Vecuronium (reduced effectiveness of neuromuscular blockade)</td>
</tr>
<tr>
<td>Phenobarbital ↔ Eslicarbazepine</td>
<td>Felbamate ↔ Phenytoin</td>
<td>Phenytoin ↔ Enteral nutrition (reduced phenytoin absorption)</td>
</tr>
<tr>
<td>Phenobarbital ↔ Lamotrigine</td>
<td>Felbamate ↔ Phenytoin</td>
<td>Phenytoin ↔ Valproate (increased phenytoin free fraction)</td>
</tr>
<tr>
<td>Phenobarbital ↔ Metronidazole</td>
<td>Felbamate ↔ Valproate</td>
<td></td>
</tr>
<tr>
<td>Phenobarbital ↔ Midazolam</td>
<td>Fluconazole ↔ Midazolam</td>
<td></td>
</tr>
<tr>
<td>Phenobarbital ↔ Nimodipine</td>
<td>Fluconazole ↔ Phenytoin</td>
<td></td>
</tr>
<tr>
<td>Phenobarbital ↔ Oxcarbazepine</td>
<td>Fluconazole ↔ Phenytoin</td>
<td></td>
</tr>
<tr>
<td>Phenobarbital ↔ Phenytoin/fosphenytoin</td>
<td>Oxcarbazepine ↔ Phenytoin</td>
<td></td>
</tr>
<tr>
<td>Phenobarbital ↔ Tolvaptan</td>
<td>Sulfamethoxazole ↔ Phenytoin</td>
<td></td>
</tr>
<tr>
<td>Phenobarbital ↔ Valproate</td>
<td>Topiramate ↔ Phenytoin</td>
<td></td>
</tr>
<tr>
<td>Phenytoin ↔ Acetaminophen</td>
<td>Valproate ↔ Lamotrigine</td>
<td></td>
</tr>
<tr>
<td>Phenytoin ↔ Atorvastatin</td>
<td>Valproate ↔ Nimodipine</td>
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<tr>
<td>Phenytoin ↔ Carbamazepine</td>
<td>Valproate ↔ Phenytoin</td>
<td></td>
</tr>
<tr>
<td>Phenytoin ↔ Dexamethasone/corticosteroids</td>
<td>Valproate ↔ Phenytoin</td>
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</tr>
<tr>
<td>Phenytoin ↔ Eslicarbazepine</td>
<td>Valproate ↔ Warfarin</td>
<td></td>
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<tr>
<td>Phenytoin ↔ Azole antifungals</td>
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<tr>
<td>Phenytoin ↔ Lamotrigine</td>
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<tr>
<td>Phenytoin ↔ Metronidazole</td>
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<td></td>
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<tr>
<td>Phenytoin ↔ Midazolam</td>
<td></td>
<td></td>
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<tr>
<td>Phenytoin ↔ Nimodipine</td>
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<td></td>
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<tr>
<td>Phenytoin ↔ Quetiapine</td>
<td></td>
<td></td>
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<tr>
<td>Phenytoin ↔ Tolvaptan</td>
<td></td>
<td></td>
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<tr>
<td>Phenytoin ↔ Topiramate</td>
<td></td>
<td></td>
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<tr>
<td>Phenytoin ↔ Valproate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenytoin ↔ Warfarin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbapenem antibiotics ↔ Valproate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine ↔ Midazolam</td>
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<td></td>
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</tbody>
</table>
drug-drug interactions may dictate preferable combinations of agents in patients with status epilepticus (Table 1-3). Most antiepileptic drugs have notable drug-drug interactions that complicate therapy, ranging from abnormal absorption to changes in protein binding, metabolism, and elimination. In many cases, these agents interact with each other, complicating matters for clinicians given that adding new agents may alter the pharmacokinetics of the current treatment regimen. Several drug-disease or drug-nutrient interactions may occur as well. Clinicians should be consistent and complete in evaluating the potential drug-drug interactions that may occur in patients who are receiving several antiepileptic drugs in the ICU environment.

Classically, phenytoin has been associated with reduced bioavailability in patients receiving enteral nutrition (Bauer 1982, Gilbert 1996). Many potential mechanisms for this interaction have been suggested, though none has definitively been proven as the primary factor. Published evidence supports this interaction in patients and in vitro models, but not in simulated clinical scenarios with healthy volunteers (Yeung 2000). Phenytoin has a prolonged GI transit time and Tmax for absorption, particularly with increasing doses (notably over 400 mg per dose) (Jung 1980). This increased GI residence of phenytoin, together with phenytoin’s potential interactions with components of enteral nutrition products, may lead to impaired enteral absorption and reduced serum phenytoin concentrations. One study that evaluated the pharmacokinetics of various phenytoin formulations (chewable tablet and suspension) in a simulated drug-nutrient interaction model suggested that phenytoin recovery was less than 40% when combined with standard enteral nutrition products (Hennessy 2003, Suzuki 2016). Of interest, the amount of phenytoin recovered differed when comparing formulas with different protein sources. Significantly greater phenytoin recovery was evident when phenytoin was combined with whey protein isolates (82%) than with casein-based isolates (48%). Other studies have postulated that phenytoin binding to protein in the nutrition product or with the enteral nutrition tubing reduces bioavailability, though more recent studies with the injectable products given enterally do not suggest this. Use of the intravenous phenytoin sodium formulation by tube does not appear to affect overall bioavailability compared with suspension in combination with nasogastric feeding in healthy volunteers. The Cmax and Tmax for the intravenous solution were greater than with the suspension (Doak 1998). Fosphenytoin solution for injection also appears to be quite well absorbed orally and may be another option for enteral use, when necessary (Kaucher 2015). In general, enteral administration of phenytoin products should be avoided in patients with status epilepticus. If conversion from intravenous to oral or enteral use is necessary, clinicians should consider separating the phenytoin dose from enteral nutrition products by at least 1 hour before and after administering or using intravenous formulations enterally (if this can be done in a way that avoids medication errors and inadvertent intravenous administration), as well as frequently monitoring serum to ensure adequate phenytoin concentrations. Clinicians should modify enteral nutrition goals to ensure patients receive the appropriate amount of calories, despite holding nutrition for phenytoin therapy.

The enteral absorption of carbamazepine and levetiracetam has also been investigated. According to the package insert

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Table 1-3. Select Significant Drug-Drug Interactions with Agents Used for Status Epilepticus (continued)

<table>
<thead>
<tr>
<th>Induction of Hepatic Metabolism (Inducing agent inducer → Drug with reduced exposure)</th>
<th>Inhibition of Hepatic Metabolism (Inhibiting agent → Drug with increased exposure)</th>
<th>Clinical Impact (additive effects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine ↔ Phenytoin</td>
<td>Partial hepatic metabolic induction (Phenytoin)</td>
<td></td>
</tr>
<tr>
<td>Carbamazepine ↔ Valproate</td>
<td>Partial hepatic metabolic induction (Phenytoin)</td>
<td></td>
</tr>
<tr>
<td>Carbamazepine ↔ Warfarin</td>
<td>Partial hepatic metabolic induction (Phenytoin)</td>
<td></td>
</tr>
<tr>
<td>Dexamethasone/corticosteroids ↔ Phenyltoin</td>
<td>Partial hepatic metabolic induction (Phenytoin)</td>
<td></td>
</tr>
</tbody>
</table>

*Drug interactions with phenobarbital are similar to those with pentobarbital.*
for carbamazepine suspension, the potential for bezoar formation with carbamazepine suspension and liquid medications or water exists. However, other studies investigating the impact of dilution of the suspension and combination with enteral nutrition products suggest little effect on carbamazepine bioavailability (Kassam 1989, Clark-Schmidt 1990). Although levetiracetam has high bioavailability with oral use, enteral administration may lead to reduced absorption by up to 30%, though levetiracetam does not appear to interact with enteral nutrition formulas; at this time, no dosage adjustment or disruption of feeds is recommended (Fay 2005, Mink 2011).

Plasma protein binding interactions may occur, changing the volume of distribution for antiepileptic drugs that are highly protein bound. Valproate competes with phenytoin for binding to albumin, resulting in phenytoin displacement, thereby increasing the concentration of free, unbound phenytoin. This functionally increases phenytoin’s volume of distribution because less phenytoin is bound to albumin and therefore constricted to the intravascular space. Of interest, however, this is not reciprocal because phenytoin does not appear to have a similar effect on valproate’s binding to albumin, though both agents affect the other’s hepatic clearance (discussed later in the text), creating a complex interplay between the two agents. Clinicians should monitor phenytoin free concentrations in this situation often to ensure that the free phenytoin concentration does not increase to supratherapeutic concentrations.

Many of the commonly used antiepileptic drugs affect the CYP enzyme system. Phenobarbital and phenytoin are two such agents, inducing enzyme activity. Concomitant use of these agents in combination with medications undergoing hepatic metabolism may reduce serum concentrations of the additive drug because of enhanced metabolism. For example, the combination of phenytoin and valproate may lead to reduced valproate concentrations by up to 50%. Maximum enzyme induction typically does not occur for 1–2 weeks, but clinicians should be wary of incremental increases in metabolic capacity as treatment evolves. Autoinduction of agents used in status epilepticus (e.g., pentobarbital and thiopental) has also been described (Wermeling 1987, Russo 1997). Conversely, CYP enzyme inhibition by agents such as valproate occurs immediately and can boost the concentration of other antiepileptic drugs such as phenytoin.

Carbapenem antibiotics increase the clearance of valproate substantially, often leading to persistently subtherapeutic valproate concentrations (up to a 70% decrease in concentrations) despite aggressive dosing (Wu 2016). Valproate is metabolized by several mechanisms in the liver, including glucuronidation, β-oxidation, and conjugation with carnitine esters. Carbapenems increase the availability of uridine diphosphate glucuronic acid, which increases valproate/glucuronide metabolite formation (Wu 2016). In addition, carbapenems appear to inhibit cytosolic glucuronidase enzymes that might unconjugate valproate (Nakamura 2008). Taken together, valproate/glucuronide metabolism is increased in the presence of carbapenems, greatly increasing systemic clearance. As a result, carbapenems should not be used in patients receiving valproate, if at all possible (Wu 2016). In patients who require carbapenems because of multidrug-resistant organisms or in patients with CNS infections, clinicians may elect to monitor serum valproate concentrations often or convert valproate therapy to an alternative agent, at least until carbapenem therapy is completed.

ICU Treatment Interactions

Additive toxicities are also common among antiepileptic drug combinations and should be considered when selecting agents. Several antiepileptic drugs can cause somnolence or disorientation (phenytoin, phenobarbital, valproate, and the benzodiazepines), particularly when used in combination. Many antiepileptic drugs may contribute to disorientation, most commonly phenytoin and the benzodiazepines. In some patients, this may manifest as delirium and prompt pharmacologic treatment, perhaps unnecessarily. Phenobarbital and other agents may cause excessive sedation, making an accurate neurological examination difficult, which can be problematic for patients with primary neurological insults such as trauma, stroke, or meningitis. Antiepileptic drugs may have significant pharmacologic interactions with other therapies commonly used in critically ill patients. For example, lacosamide in combination with β-blockers, calcium channel blockers, or fentanyl may prolong the PR interval and potentiate bradycardia (Luk 2012).

The combination of valproate and topiramate may increase the risk of hyperammonemia in some patients. Hyperammonemia secondary to valproate may occur as often as 40% in patients receiving valproate for prolonged durations, with changes in carnitine balance being evident within the first 7 days of therapy (Morand 2012). The overall incidence of hyperammonemia with acute use appears to be low, though hyperammonemia rates may be higher than expected in the critically ill population (Cook 2016). Valproate inhibits a critical enzyme in carnitine synthesis (carbamoyl phosphate synthetase-I [CPS-I]). Inhibition of CPS-I leads to accumulation of ammonia, rather than elimination as carbamoyl phosphate (Morand 2012). Renal elimination of valproylcarnitine is elevated early in therapy as well. Proactively monitoring ammonia concentrations in patients requiring prolonged valproate therapy or those who are critically ill is prudent. Although this adverse effect of valproate is well documented, it appears to be increased in severity and frequency when valproate is used in combination with topiramate. The etiology of this interaction has yet to be shown. Some patients with elevated ammonia concentrations may require carnitine supplementation to treat or prevent hyperammonemia (Lheureux 2009). The typical dose of intravenous levocarnitine for valproate-associated hyperammonemia is a 100-mg/kg loading dose followed by 50 mg/kg/day (up to 3 g/day) (Mock 2012). Patients with
concomitant malnutrition or hepatic dysfunction may merit more proactive monitoring for this adverse effect.

With acute exposure, phenytoin may potentiate the effects of nondepolarizing neuromuscular blockers such as vecuronium, and chronic exposure to phenytoin may result in neuromuscular blocker “resistance” (Gray 1989). In this situation, patients lack response to nondepolarizing neuromuscular blockers and require escalating doses to ensure adequate blockade. Various mechanisms have been proposed, though two separate causes seem most likely. First, phenytoin is a known CYP enzyme inducer that appears to induce the metabolism of the aminosteroid neuromuscular blockers (e.g., vecuronium), reducing the serum concentration and, hence, the therapeutic effect (Soriano 2004). Second, phenytoin produces mild neuromuscular blockade, potentially leading to the up-regulation of neuromuscular and extrajunctional acetylcholine receptors, which would also lead to reduced pharmacologic response to neuromuscular blocking agents at typical doses (Soriano 2004). Benzylisoquinoline agents (metabolized by Hofmann elimination, hence bypassing CYP), as opposed to aminosteroids, do not appear to restore sensitivity to neuromuscular blockade, suggesting that the up-regulation of acetylcholine receptors plays a significant role in neuromuscular blocker resistance (Richard 2005).

Topiramate is a weak carbonic anhydrase inhibitor that can reduce serum bicarbonate, disrupting the acid-base balance in critically ill patients (Table 1-1). Chronic topiramate use results in metabolic acidosis in up to 48% of patients with ambulatory epilepsy (Garris 2005, Jovanovic 2014). Limited published experience is available, but initial indications suggest metabolic acidosis is not a significant factor with acute topiramate therapy in the more critically ill status epilepticus population (Hottinger 2012, Synowiec 2012). The limited reporting to this point is likely a combination of publication bias, lack of experience with topiramate in status epilepticus, and the fact that clinicians likely work around the metabolic acidosis as indicated.

Pharmacokinetic Alterations
The oral or enteral route is not preferred for most antiepileptic drugs because of their variability in absorption. Often, this variability occurs because of the properties of the drug itself, though patients with gastric and intestinal dysmotility may also have fluctuations in enteral absorption. Oral or enteral doses of antiepileptic drugs typically do not achieve peak concentrations as high or as quickly as when given intravenously. Thus, oral/enteral doses may delay the time to effect for many of these agents. Patients who receive intravenous opioids during ICU care or pentobarbital for refractory status epilepticus may have reduced GI motility, as may patients receiving vasopressors and those with a TBI. Alterations in GI motility should be accounted for when considering changing intravenous therapy to oral or enteral therapy in patients with status epilepticus.

Alterations in volume of distribution are common in critically ill patients, including those with status epilepticus, often because of aggressive fluid resuscitation in clinical scenarios such as trauma or sepsis. Plasma protein concentrations such as albumin also decrease after the onset of critical illness, including the acute phase of status epilepticus, as part of the negative acute-phase response. Hypoalbuminemia leads to an increased fraction unbound of medications that are highly protein bound (greater than 80%). Although the proportion of free drug is higher in this situation, overall drug exposure is typically unchanged because of increased metabolism of the unbound fraction (Benet 2002). This phenomenon may reduce total serum drug concentrations, leading to misinterpretation of serum concentrations and inappropriate dose adjustments. Correction equations are available for clinicians to use, correcting for the serum albumin concentration and estimating the fraction unbound drug for both phenytoin and valproate, though the correlation of these equations with the actual fraction unbound is not always accurate (Mlynarek 1996, Winter 2004, Hermida 2005). Of note, these equations primarily estimate the fraction unbound because of hypoalbuminemia and do not account for protein-binding displacement drug interactions.

Phenytoin and valproate are significantly affected by hypoalbuminemia. Clinically, if the provider solely monitors total phenytoin concentrations, the concentration may appear to be below the normal desired range, and dose increases may be made inappropriately. Ideally, total and free concentrations will be available to define a specific patient’s fraction of unbound drug, preventing inappropriate dose adjustments. Alternatively, clinicians may elect to monitor only free phenytoin concentrations. Valproate is another highly protein-bound agent that may have altered serum concentrations because of hypoalbuminemia. The clinical relevance of these changes is less well understood, however, because of the lack of availability of free valproate assays in some institutions and paucity of literature describing the phenomenon. In theory, valproate’s alterations may be more complex in the context of hypoalbuminemia. Valproate, unlike phenytoin, has saturable protein binding at clinically attainable concentrations (Hermida 2005, Panomvana Na Ayudhya 2006). In patients with normal albumin concentrations, this saturation is typically evident only at supratherapeutic concentrations. However, in patients with hypoalbuminemia, the saturation threshold is likely at lower doses and may occur at serum concentrations within the normal desired range. Clinicians should consider the potential impact of increased fraction unbound drug with valproate dosing, particularly in patients who have hypoalbuminemia and those who do not seem to...
have substantially increased total serum concentrations after loading doses are administered.

Physiologic response to critical illness can affect the pharmacokinetics of antiepileptic drugs in patients with status epilepticus. Patients with a TBI have increases in metabolic capacity over at least the first 10 days after injury. This is likely because of the various anti-inflammatory cytokines released after injury such as interleukin-2 and protein provision (McKindley 1997, Boucher 1998, Kalsotra 2003). Clearance of phenytoin and other heptatically metabolized antiepileptic drugs is increased after brain injury. For instance, phenytoin Vmax increases almost 4-fold from baseline after brain injury, increasing the initial inhibition of phenytoin metabolism and then the subsequent induction of metabolism (McKindley 1997). The hepatic metabolism of other antiepileptic drugs is also altered. Over time, proinflammatory cytokines release, and changes in perfusion may reduce hepatic metabolism in certain patients, particularly those early in sepsis and those with cardiac dysfunction (McKindley 1997). Overall, increased hepatic metabolism of antiepileptic drugs should be anticipated in critically ill individuals with status epilepticus.

Renal clearance may also affect the pharmacokinetics of antiepileptic drugs in the context of status epilepticus. Augmented renal clearance has been described in patients with a TBI, subarachnoid hemorrhage, and intracranial hemorrhage, as well as other conditions in which status epilepticus may be common (Udy 2010, Udy 2011, May 2015, Morbitzer 2016). Few of the antiepileptic drugs used in status epilepticus are renally eliminated, with levetiracetam as the prime exception. Levetiracetam concentrations in patients with augmented renal clearance are well below predicted values, leading to suboptimal drug exposure, and agents with comparable pharmacokinetics, such as gabapentin, may be similarly affected. Clinicians should consider the value of therapeutic drug monitoring for agents like levetiracetam in patients who may have augmented renal clearance in order to optimize dosing and drug exposure.

**Drug-Induced Seizures**

Drug-induced seizures are an important consideration in critically ill patients with status epilepticus. Patients with a severe TBI, stroke, or meningitis may have blood-brain barrier inflammation that permits increased drug penetration into the CNS and may lead to seizures even at “normal” serum concentrations. Typically, agents known to lower the seizure threshold or cause seizures may be problematic in these patients, and the clinician must evaluate the risk of drug-induced seizures when using these agents. Patients with advanced age (older than 60 years), low body weight, or diminished renal function may also be at higher risk of drug-induced seizures because of increased drug exposure. Patients with toxicological emergencies, such as those who have ingested large doses of antiepileptic drugs, may present with supratherapeutic concentrations of these medications, potentially inducing seizures, even with medications not associated with seizures at normal concentrations. Several medications commonly used in ICU patients have been associated with drug-induced seizures in non-toxicological situations, including β-lactam antibiotics, antipsychotics, antidepressants, and analgesics such as tramadol and meperidine.

β-Lactams have long been associated with seizures. High-dose penicillin G, cefepime, and imipenem are classically linked with drug-induced seizures, although almost all β-lactams have been implicated (Grondahl 1993, Lam 2006, Cannon 2014). β-Lactams mildly inhibit GABA, likely by the β-lactam ring. Several factors appear to govern the likelihood of a specific β-lactam agent causing seizures. Subtle differences in lipophilicity and possibly the unique side chains on each agent may determine each agent’s seizure-provoking potential (De Sarro 1995). The overall seizure rate in study populations appears to be about 0.15%–0.68% with non-carbapenem β-lactams and 0.4%–0.68% with carbapenems (Cannon 2014). A meta-analysis of randomized controlled trials suggests that carbapenems are associated with a significantly higher risk of seizures than non-carbapenem antibiotics (OR 1.87; 95% CI, 1.35–2.59) (Cannon 2014). The carbapenem imipenem has most been associated with seizures compared with non-carbapenem antibiotics (four additional events per 1000 patients). Of note, however, imipenem was no more likely to induce seizures than other carbapenems. Cephalosporins (cefepime and ceftriaxone) and the carbapenems are commonly used in the neurocritical care population and for those with CNS infection, both of which are high-risk populations for drug-induced seizures and status epilepticus. The precise rate of seizures with these agents is unknown, though patients with impaired renal function and those receiving high doses appear to be at higher risk (Lam 2006).

Clinicians should also be wary of using other agents associated with drug-induced seizures, particularly in patients who have other risk factors for seizures such as TBI, stroke, or sepsis (Pisani 2002). Antipsychotic agents such as haloperidol are commonly used in the ICU for acute delirium or as continuation of home therapy. Haloperidol is associated with a lowered seizure threshold, though primarily with chronic therapy rather than intermittent acute therapy (Minabe 1988). Atypical antipsychotics commonly used in the ICU such as olanzapine and quetiapine may be considered at intermediate risk of inducing seizures as well (Alldredge 1999). Although tricyclic antidepressants are classically associated with seizures (particularly in toxicological scenarios), bupropion is most often associated with drug-induced seizures (1.4% annual cumulative seizure risk in outpatients) (Rosenstein 1993). Analgesics such as tramadol and meperidine lower the seizure threshold at normal therapeutic doses and should be used sparingly in patients at risk of seizures, when possible (Marinella 1997, Potschka 2000, Seifert 2004, Schlick 2015).
Successful treatment of status epilepticus often leaves clinicians with important decisions to make as the patient prepares for discharge. Evidence is sparse to guide clinicians on the appropriate method for tapering antiepileptic drugs, and no definitive guide exists regarding which agents should preferentially be discontinued if the antiepileptic regimen is to be streamlined. Practically, patients who were admitted with a history of a seizure disorder and who were already taking antiepileptic drugs at home should be continued on their home regimen, provided that adherence is addressed with the patient and the patient’s family. Clinicians should ensure that the agents were being tolerated and can feasibly be obtained by the patient so that continued adherence is possible. The dose of these home medications may need to be optimized at discharge. Most patients who are admitted for status epilepticus are discharged on one or two antiepileptic drugs (and for patients with a history of seizures, at least one additional agent in combination with their previous home regimen) (Cook 2012). Typically, these agents were initiated in the midst of status epilepticus treatment and converted to oral formulations. A rational approach for selecting which antiepileptic drugs to continue after status epilepticus may be similar to how combinations of urgent therapies are evaluated. Clinicians should consider selecting agents with different or complimentary mechanisms of action that do not have significant overlapping toxicities. Patients requiring tapering and modification of the antiepileptic regimen after discharge should be referred to a neurologist.

FUTURE DIRECTIONS

There are gaps in the evidence regarding the impact of timing of urgent therapy agents and the optimal urgent therapy antiepileptic drugs to use, both in the acute phase and for chronic therapy after discharge. The role of pharmacologic coma for refractory status epilepticus continues to be evaluated, and more information is needed on the optimal timing for initiating this method of treatment and ways to maximize its safety. The role of newer agents on the horizon for status epilepticus such as allopregnanolone and ketamine needs to be formally evaluated in well-designed clinical trials.

CONCLUSION

Treatment success in status epilepticus is primarily based on rapidly using the appropriate agents at optimal doses. Emergency therapy typically includes benzodiazepines such as lorazepam or midazolam. There are gaps in the evidence regarding the impact of timing of urgent therapy agents and the optimal urgent therapy antiepileptic drugs to use, both in the acute phase and for chronic therapy after discharge. The role of pharmacologic coma for refractory status epilepticus continues to be evaluated, and more information is needed on the optimal timing for initiating this method of treatment and ways to maximize its safety. The role of newer agents on the horizon for status epilepticus such as allopregnanolone and ketamine needs to be formally evaluated in well-designed clinical trials.

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Herzog AG. Catamenial epilepsy: update on prevalence, pathophysiology and treatment from the findings of the NIH Progesterone Treatment Trial. Seizure 2015;28:18-25.


Self-Assessment Questions

1. A 54-year-old Hispanic man presents with a history of a fall. On admission, his CT reveals traumatic subarachnoid hemorrhage. During the CT, the patient has generalized tonic-clonic seizure activity for 10 minutes. His medical history includes active treatment for tuberculosis. His vital signs and laboratory values are as follows: temperature 98.2°F (36.8°C), heart rate 111 beats/minute, blood pressure 128/63 mm Hg, respiratory rate 21 breaths/minute, SaO₂ 100%, serum sodium 144 mEq/L, serum potassium 4.7 mEq/L, BUN 9 mg/dL, Scr 0.89 mg/dL, glucose 115 mg/dL, serum magnesium 2.2 mg/dL, serum phosphorus 2.1 mg/dL, and ethanol 150 mg/dL. His urine drug screen is positive for benzoylecgonine. Which one of the following is best to recommend for this patient?
   A. Valproate for traumatic brain injury (TBI)
   B. Thiamine for acute ethanol intoxication
   C. Pyridoxine for isoniazid therapy
   D. Ketamine for cocaine overdose

2. Which one of the following therapies would be best for L.S. as he arrives in the ED?
   A. Give lorazepam 4 mg intravenously × 1.
   B. Give midazolam 5 mg intramuscularly × 1.
   C. Give diazepam 10 mg intramuscularly × 1.
   D. No therapy is necessary in transit.

3. Which one of the following is most likely to have contributed to L.S.’s presentation with status epilepticus?
   A. Methamphetamine use
   B. Electrolyte abnormalities
   C. Medication toxicity
   D. History of epilepsy

4. Which one of the following components of L.S.’s initial intravenous fluids is most important to supplement early in his care?
   A. Magnesium
   B. Potassium
   C. Dextrose
   D. Sodium

5. P.R. is a 54-year-old man (height 65 inches [166 cm], weight 40 kg) who presents to the ED with fever, altered mental status, and nuchal rigidity. His medical history includes chronic obstructive pulmonary disease and diabetes. His family reports that P.R. has a penicillin allergy (rash). He is immediately initiated on dexamethasone, vancomycin, and meropenem after a lumbar puncture. On day 1 of his ICU admission, P.R.’s Glasgow Coma Scale score decreases from 3-6-1T to 2-4-1T. An EEG reveals nonconvulsive status epilepticus. His CSF culture is positive for Haemophilus influenzae (β-lactamase positive). On ICU day 1, P.R.’s vital signs and laboratory values are as follows: temperature 100.8°F (38.2°C), heart rate 103 beats/minute (normal sinus), blood pressure 98/45 mm Hg, respiratory rate 18 breaths/minute (ventilator rate 15 breaths/minute), SaO₂ 94%, serum sodium 137 mEq/L, serum potassium 4.0 mEq/L, BUN 12 mg/dL, SCr 1.29 mg/dL, glucose 135 mg/dL, serum magnesium 1.9 mg/dL, serum phosphorus 3.7 mg/dL, and fraction of inspired oxygen (Fio₂) 70%.

   Which one of the following is best to recommend regarding the use of neuromuscular blocking agents in P.R.?
   A. Vecuronium should be avoided.
   B. Cisatracurium is less likely to have resistance.
   C. Phenytoin should be changed to valproate to avoid interaction with neuromuscular blockers.
   D. Higher doses of a neuromuscular blocking agent may be necessary.

6. Which one of the following would best optimize P.R.’s antimicrobial therapy?
   A. Change meropenem to cefepime.
   B. Change meropenem to ceftriaxone.
   C. Change meropenem to imipenem/cilastatin.
   D. Continue meropenem.

Questions 2–4 pertain to the following case.

L.S. is a 22-year-old man (height 70 inches, weight 81 kg) with a history of epilepsy, substance abuse, and depression. When emergency medical services arrives, L.S. still has seizure-like activity. He has no known allergies to medications. L.S.’s vital signs and laboratory values are as follows: temperature 98.8°F (37.1°C), heart rate 98 beats/minute, blood pressure 138/64 mm Hg, respiratory rate 23 breaths/minute, SaO₂ 98%, serum sodium 139 mEq/L, serum potassium 3.7 mEq/L, BUN 9 mg/dL, Scr 1.13 mg/dL, glucose 155 mg/dL, serum magnesium 1.2 mg/dL, serum phosphorus 2.7 mg/dL, and ethanol 0 mg/dL. His urine drug screen is positive for bupropion, methamphetamine, and oxycodone. L.S.’s sister arrives in the ED with a medication list that confirms he takes bupropion extended release 150 mg daily and lamotrigine 100 mg twice daily at home.

2. Which one of the following therapies would be best for L.S. as he arrives in the ED?
   A. Give lorazepam 4 mg intravenously × 1.
   B. Give midazolam 5 mg intramuscularly × 1.
   C. Give diazepam 10 mg intramuscularly × 1.
   D. No therapy is necessary in transit.

3. Which one of the following is most likely to have contributed to L.S.’s presentation with status epilepticus?
   A. Methamphetamine use
   B. Electrolyte abnormalities
   C. Medication toxicity
   D. History of epilepsy

Questions 5–8 pertain to the following case.

P.R. is a 54-year-old man (height 65 inches [166 cm], weight 40 kg) who presents to the ED with fever, altered mental status, and nuchal rigidity. His medical history includes chronic obstructive pulmonary disease and diabetes. His family reports that P.R. has a penicillin allergy (rash). He is immediately initiated on dexamethasone, vancomycin, and meropenem after a lumbar puncture. On day 1 of his ICU admission, P.R.’s Glasgow Coma Scale score decreases from 3-6-1T to 2-4-1T. An EEG reveals nonconvulsive status epilepticus. His CSF culture is positive for Haemophilus influenzae (β-lactamase positive). On ICU day 1, P.R.’s vital signs and laboratory values are as follows: temperature 100.8°F (38.2°C), heart rate 103 beats/minute (normal sinus), blood pressure 98/45 mm Hg, respiratory rate 18 breaths/minute (ventilator rate 15 breaths/minute), SaO₂ 94%, serum sodium 137 mEq/L, serum potassium 4.0 mEq/L, BUN 12 mg/dL, SCr 1.29 mg/dL, glucose 135 mg/dL, serum magnesium 1.9 mg/dL, serum phosphorus 3.7 mg/dL, and fraction of inspired oxygen (Fio₂) 70%.

5. P.R.’s team decides that neuromuscular blockade is needed to facilitate mechanical ventilation. Which one of the following is best to recommend regarding the use of neuromuscular blocking agents in P.R.?
   A. Vecuronium should be avoided.
   B. Cisatracurium is less likely to have resistance.
   C. Phenytoin should be changed to valproate to avoid interaction with neuromuscular blockers.
   D. Higher doses of a neuromuscular blocking agent may be necessary.

6. Which one of the following would best optimize P.R.’s antimicrobial therapy?
   A. Change meropenem to cefepime.
   B. Change meropenem to ceftriaxone.
   C. Change meropenem to imipenem/cilastatin.
   D. Continue meropenem.
7. Which one of the following factors is most likely to increase P.R.’s risk of drug-induced seizures?
   A. Dexamethasone use
   B. Meropenem use
   C. Vancomycin use
   D. Age

8. Which one of the following best describes the combination of phenytoin with P.R.’s current meningitis regimen?
   A. It is likely to accumulate if vancomycin causes nephrotoxicity.
   B. Its metabolism is inhibited by meropenem, and it will have higher total concentrations.
   C. Its metabolism is induced by dexamethasone, and it will have lower total concentrations.
   D. It will have altered protein binding because of concomitant vancomycin.

Questions 9 and 10 pertain to the following case.
J.B. is a 64-year-old woman who presents with a 2-week history of progressive neurologic decline after a fall. She was brought to the hospital by her family, who noted that J.B. could not open doors or hold utensils with her right hand. A CT reveals a left temporal chronic subdural hematoma. J.B. has a medical history of hypothyroidism, atrial fibrillation, hyperlipidemia, and hypertension. She was adherent to her home drugs: metoprolol, levothyroxine, apixaban, and aspirin. J.B. undergoes a burr hole washout to evacuate her chronic subdural hematoma. On hospital day 2, just after eating lunch, she has a generalized tonic-clonic seizure for about 7 minutes, which is treated with lorazepam 4 mg intravenously × 1. She is currently postictal and unable to communicate. Her neurosurgeons wish to initiate an intravenous antiepileptic drug to prevent further seizures. J.B.’s vital signs and laboratory values are as follows: temperature 99°F (37.2°C), heart rate 88 beats/minute, blood pressure 100/49 mm Hg, respiratory rate 18 breaths/minute (ventilator rate 12), Sao₂ 99%, serum sodium 145 mEq/L, serum potassium 3.8 mEq/L, BUN 10 mg/dL, SCR 0.89 mg/dL, glucose 153 mg/dL, serum magnesium 2.1 mg/dL, serum phosphorus 2.7 mg/dL, arterial pH 7.34, Pco₂ 33 mm Hg, Po₂ 126 mm Hg, HCO₃⁻ 24 mEq/L, Fio₂ 40%, and total phenytoin 11.2 mg/L.

9. Which one of the following is best to recommend for J.B.?
   A. Phenytoin
   B. Valproate
   C. Levetiracetam
   D. Lacosamide

10. Which one of the following statements best describes adding antiepileptic drugs if J.B.’s status epilepticus continues?
    A. Agents for urgent therapy should be added rapidly.
    B. Urgent therapy agents with overlapping mechanisms should be used preferentially.
    C. Escalation to agents used for refractory therapy is necessary if the initial urgent therapy fails.
    D. Benzodiazepine therapy should not be repeated after the initial emergency therapy period.

Questions 11 and 12 pertain to the following case.
M.R. is a 32-year-old man (height 74 inches [188 cm], weight 80 kg) who presented with a severe TBI after a motor vehicle collision. He has no contributory medical history other than social anxiety disorder. On admission, M.R. was taken to the operating room for a subdural hematoma evacuation; since then, he has convalesced in the ICU. He was initiated on phenytoin for posttraumatic seizure prophylaxis. On ICU day 3, M.R.’s neurologic examination worsened subtly; hence, the neurocritical care team obtained a CT of his head and a continuous EEG. The EEG revealed nonconvulsive status epilepticus. M.R. was given an intravenous benzodiazepine, and a total phenytoin concentration was obtained. On ICU day 3, his vital signs and laboratory values are as follows: temperature 98.4°F (36.9°C), heart rate 88 beats/minute, blood pressure 100/49 mm Hg, respiratory rate 18 breaths/minute (ventilator rate 12), Sao₂ 99%, serum sodium 145 mEq/L, serum potassium 3.8 mEq/L, BUN 10 mg/dL, SCR 0.89 mg/dL, glucose 153 mg/dL, serum magnesium 2.1 mg/dL, serum phosphorus 2.7 mg/dL, arterial pH 7.34, Pco₂ 33 mm Hg, Po₂ 126 mm Hg, HCO₃⁻ 24 mEq/L, Fio₂ 40%, and total phenytoin 11.2 mg/L.

11. Which one of the following is best to recommend for M.R.’s refractory status epilepticus?
    A. Valproate 30-mg/kg load plus 1-mg/kg/hour infusion
    B. Propofol 50-mcg/kg/minute infusion
    C. Midazolam 0.05-mg/kg/hour infusion
    D. Ketamine 100-mg load plus 1-mg/kg/hour infusion

12. Which one of the following would best monitor the efficacy of pentobarbital therapy in M.R.?
    A. Serum pentobarbital concentrations
    B. Continuous EEG
    C. Bispectral index
    D. Glasgow Coma Score

Questions 13–15 pertain to the following case.
D.B. is a 42-year-old woman (weight 70 kg) with a history of treatment-refractory epilepsy. Her current home antiepileptic regimen consists of lamotrigine 100 mg twice daily, clonazepam 1 mg twice daily, and phenytoin 300 mg once daily. While D.B. was at work, emergency medical services were called because of intermittent seizure activity. She was initiated on phenytoin for posttraumatic seizure prophylaxis. On ICU day 3, her vital signs and laboratory values are as follows: temperature 99°F (37.2°C), heart rate 63 beats/minute (normal sinus), blood pressure 126/65 mm Hg, respiratory rate 14 breaths/minute, and Sao₂ 97%.

13. Which one of the following agents would be best as emergency status epilepticus therapy for D.B.?
    A. Levetiracetam 1000 mg intravenously × 1
    B. Fosphenytoin 20 mg/kg intravenously × 1
    C. Ketamine 1 mg/kg intravenously × 1
    D. Lorazepam 4 mg intravenously × 1

14. D.B.’s home antiepileptic regimen is reinitiated, and she is given the therapy you selected from the previous question; however, she continues to have seizures on EEG. The neurologists would like to initiate valproate. Which
one of the following is the most important consideration regarding adding valproate for D.B.?
A. Free phenytoin concentrations should be obtained within 24 hours of valproate initiation.
B. The phenytoin dose will likely have to be increased within 24 hours of valproate initiation.
C. Free valproate concentrations should be obtained within 24 hours of valproate initiation.
D. Valproate will decrease the possibility of lamotrigine-associated rash.

15. For D.B., which one of the following ancillary laboratory values would be most important to obtain during the first 2–3 days of valproate therapy?
A. Plt
B. γ-Glutamyl transferase
C. WBC
D. Ammonia