



## **Management of the ED Patient in Status Epilepticus**

Edward Sloan, MD, MPH, FACEP

A 37-year old male is brought to the emergency department by EMS because of a seizure at home. The patient had a generalized tonic-clonic seizure prior to going to bed. The seizure lasted for approximately ten minutes, followed by a period of unresponsiveness during EMS transport. The patient has a long history of post-traumatic seizures that are managed with phenytoin and phenobarbital. There has been neither recent illness nor recent head trauma.

In the emergency department, the patient is still unresponsive. There are no focal neurological findings or any evidence of any other medical condition that would precipitate a seizure. The patient then goes on to have another seizure in the Emergency Department. The seizure is generalized with tonic-clonic seizure activity. The seizure lasts for over two minutes while medications are being obtained.

**Key Clinical Questions:**

What % of ED seizure patients will not respond to initial treatment with benzodiazepines?

Is there a difference in outcome in patients treated with diazepam vs. lorazepam?

What is the role of the following therapies in patients who continue to seize after being administered full, weight based doses of benzodiazepines?

IV phenytoins?

IV phenobarbital?

IV valproic acid?

IV propofol?

IV continuous benzodiazepine infusions?

IV pentobarbital?

## Management of the ED Patient in Status Epilepticus

### Epidemiology

There are an estimated 2.5 million patients with epilepsy in the US, based on a prevalence of about 6.6 per 1000 Americans.<sup>1</sup> Up to 28% of all epilepsy patients require treatment in Emergency Departments annually.<sup>2</sup> In addition to these patients who have an established seizure diagnosis, another 150,000 patients are newly diagnosed with a seizure, and most are treated in the Emergency Department at some time during this process.<sup>3</sup> A recent multi-center ED study has demonstrated that 1-2% of all ED patients is being treated for a complaint related to seizures.<sup>4</sup> Applying this percentage to the 100 million ED visits recorded in 1995, up to two million patients are treated annually for seizures in the ED.<sup>5</sup>

Status epilepticus (SE) occurs in 50-150,000 patients per year (based on an incidence of 50 per 100,000 Americans), and is most common at the extremes of age.<sup>6,7</sup> The reported mortality rate for patients in SE ranges from 5-22%, and has been reported to be as high as 65% in those whose SE is refractory to first line therapies.<sup>6-10</sup> Status epilepticus is seen in up to 7% of ED seizure patients, and a survey reported that at least five SE patients are treated annually by each Emergency Medicine physician.<sup>4,11</sup>

### **What percent of ED seizure patients will not respond to initial treatment with benzodiazepines? Does efficacy differ between diazepam and lorazepam?**

These questions address how often patients should be expected not to respond to the initial EMS or ED therapy with benzodiazepines.

There are data from uncontrolled studies that determine the rate of active seizing and SE are seen in the ED. The multi-center prospective study by Huff reported a 17% seizure recurrence rate among all ED seizure patients, and a 6% prevalence of SE in these ED patients.<sup>4</sup> A retrospective study of EMS patients reported a 7% rate of active seizing among all EMS seizure patients, and a 1% active seizure rate at the time of ED admission.<sup>12</sup> A retrospective review of adult seizure patients demonstrated a 1.5% rate of active seizing at the time of ED admission.<sup>5</sup> Retrospective studies of ED pediatric seizure patients reported that 5-7% of these patients will seize while in the ED, regardless of the etiology, febrile vs. afebrile seizure.<sup>13-15</sup>

Four prospective randomized studies compare the use of IV diazepam and IV lorazepam in the treatment of SE. Leppik's 1983 study of 78 patients demonstrated seizure control in 89% of lorazepam-treated patients and 76% of diazepam-treated patients, a difference that was noted not to be statistically different.<sup>16</sup> A 1995 pediatric study of lorazepam and diazepam from the UK demonstrated that a single dose of lorazepam was able to terminate seizures or SE in 76% of patients, and that a single dose of diazepam was effective in 51% of patients.<sup>17</sup> In this pediatric population, respiratory complications were noted in 15% of diazepam-treated patients and 3% of lorazepam-treated patients. Treiman compared the use of lorazepam with diazepam and phenytoin in a VA study of patients in SE.<sup>10</sup> This 1998 study of 384 patients, which also did not focus specifically on ED patients, reported effective termination of clinical seizing and EEG

evidence of seizures at 20 minutes in 67% of those treated with lorazepam and 60% of those treated with diazepam and phenytoin. The pre-hospital trial of SE, published in 2001, compared the use of lorazepam (2 mg IVP x 2), diazepam (5mg IVP x 2), and placebo.<sup>18</sup> This study demonstrated SE termination in 59% of lorazepam-treated patients, 43% of diazepam-treated patients, and 21% of patients who received neither of these anti-epileptic therapies in the EMS setting. These data demonstrated a 1.9x greater odds of SE termination in patients treated with lorazepam vs. those treated with diazepam, with complication rates of 10% in both treatment groups. In addition to these prospective studies, Treiman also noted that benzodiazepines have been found to effectively treat 79% of 1,346 SE patients analyzed from uncontrolled clinical studies.<sup>19</sup>

### **Conclusions:**

1. Up to 2% of all ED patients will present because of problems related to a seizure disorder.
2. 5-17% of all seizure patients will seize while in the Emergency Department.
3. 6% of ED patients will be classified as having SE.
4. Lorazepam is expected to terminate seizures and SE in 59-89% of seizure patients
5. Diazepam is expected to terminate seizures and SE in 43-76% of seizure patients.
6. The use of lorazepam in pediatric patients with seizures and SE is associated with fewer pulmonary complications than is the use of diazepam.

**What is the role of the following second line therapies in SE patients: IV phenytoins? IV phenobarbital? IV valproate? IV propofol? IV continuous benzodiazepine infusions? IV pentobarbital?**

### **IV Phenytoins:**

Although IV phenytoin is an accepted therapy for patients whose seizures cannot be successfully terminated with benzodiazepines, few controlled trials have addressed its use in SE. The 1998 Treiman VA study, as mentioned before, showed a 56% success in terminating SE using a diazepam/phenytoin combination.<sup>10</sup> The 1988 Shaner study evaluated the use of diazepam and phenytoin in 18 patients in a clinical trial comparing this regimen with 18 patients treated with phenobarbital.<sup>20</sup> The use of diazepam and phenytoin was associated with longer seizure duration than with the use of phenobarbital (5 vs. 9 minutes,  $p < .06$ ). Complications in these two treatment groups were comparable. In a published abstract, IV fosphenytoin was studied in ED SE patients, most of who were treated with benzodiazepines prior to receiving their fosphenytoin infusion.<sup>21</sup> Following the infusion of fosphenytoin, which could occur at rates up to 150 mg PE/min, 97% were noted to remain seizure-free during the two-hour observation period. There

have been no published prospective studies of fosphenytoin in the treatment of SE patients who have failed benzodiazepine treatment.

The issue of high-dose phenytoins in the treatment of SE is only addressed in one case series and one published guideline.<sup>22;23</sup> Osorio reported that of 13 SE patients who were given high-dose phenytoin (mean dose 24 mg/kg), five (38%) did not require pentobarbital therapy. The Epilepsy Foundation of America's Working Group on SE recommends that up to 30/mg/kg of phenytoin be given prior to using another AED.

### **Conclusions:**

1. The combination of diazepam and phenytoin will terminate between 38 and 56% of seizures in patients with SE.
2. No published articles demonstrate any enhanced efficacy of fosphenytoin over phenytoin.
3. One case series suggests that high dose phenytoin may be useful in SE patients.
4. The Epilepsy Foundation of America Consensus Guideline suggests that high dose phenytoins may be effective in treating SE.

### **IV Phenobarbital:**

The use of IV phenobarbital is commonly accepted as a therapy for patients who fail to respond to benzodiazepines and who are in SE. Two non-blinded studies have examined the efficacy of this drug in seizures and SE. The 1988 Shaner study compared the use of diazepam and phenytoin with the use of phenobarbital and optional phenytoin in 36 patients in SE.<sup>20</sup> SE duration was noted to be shorter with the use of phenobarbital (5 vs. 9 minutes,  $p < .06$ ), and 61% of phenobarbital patients did not require the addition of phenytoin in order to terminate SE. Complication rates were comparable in the two treatment groups, suggesting phenobarbital as an alternative to the use of diazepam and phenytoin. The second phenobarbital study by Painter compared phenytoin with phenobarbital in the treatment of neonatal seizures.<sup>24</sup> This study demonstrated comparable efficacy, with 43% efficacy with phenobarbital and 45% efficacy with phenytoin. Combined treatment with both agents increased the efficacy in treating seizures and SE to 57-62% in these neonatal patients.

### **Conclusions:**

1. Phenobarbital is comparable to the use of diazepam in phenytoin in the termination of seizures and SE.
2. 43-61% of patients with seizures and SE are effectively with phenobarbital.
3. When used with phenytoin, phenobarbital will effectively treat 57-62% of seizures and SE.

### **IV Valproate:**

IV valproate has been shown to be effective in one 1993 French study of SE patients.<sup>25</sup> In this study, valproate was used to treat SE patients irrespective of initial anti-epileptic drug therapy, and seizure termination was achieved within 20 minutes of infusion for 83% of the SE patients. Another European study, from Spain, demonstrated 58% control of SE in pediatric patients with SE.<sup>26</sup> IV valproate has also been reported in other case series to be effective in the treatment of myoclonic seizures and generalized convulsive and non-convulsive SE in the US.<sup>27-29</sup> In the 2000 Limdi study, 16 of 20 patients were effectively treated with a rapid infusion of valproate for intractable seizures. In the 2000 Sinha study, 13 hypotensive geriatric patients were effectively infused with IV valproate with an exacerbation of their hypotension. Another US study by Venkataraman demonstrated that IV valproate could be infused at rates up to 6 mg/kg/min, or up to 300 mg/min, although this was not studied in the setting of SE.<sup>30</sup>

### **Conclusions:**

1. When used for the treatment of SE, valproate will control seizures in 58-83% of patients.
2. IV valproate has been shown to be infused without hypotension in geriatric patients and at rapid rates in pediatric patients.

### **IV Propofol:**

IV propofol has been reported to be effective in an EMS case report from Finland, as well as in hospitalized patients from Switzerland and the West Indies.<sup>31-33</sup> This drug is thought to provide burst suppression in patients with refractory SE, and it can be used in the ED. In one US study of 16 patients that compared propofol with high-dose barbiturates, propofol was noted to terminate fewer cases of SE (63 vs. 82%,  $p = \text{NS}$ ), but the time to termination was much shorter with the use of propofol (3 vs. 123 min,  $p < .002$ ).<sup>34</sup> In a study of 20 refractory SE patients from Virginia, the use of propofol was compared with midazolam.<sup>35</sup> Propofol achieved a 64% rate of clinical seizure suppression, as compared to 67% for midazolam. Mortality, however, tended to be higher with propofol (57 vs 17%,  $p = .16$ ), especially in those with an APACHE II score  $\geq 20$ .

### **Conclusions:**

1. The use of propofol provides a 63-64% efficacy in treating SE patients.
2. Propofol may be less effective than high-dose barbiturates, and comparable to the use of midazolam in the treatment of SE patients.
3. Propofol may be associated with a higher mortality than the use of midazolam in more critically ill patients.

## **IV Continuous Benzodiazepine Infusions:**

The continuous infusion of benzodiazepines has been used to treat both pediatric and adult patients with refractory SE. In one open-label study in 40 pediatric patients, the continuous infusion of diazepam and midazolam was compared, with the endpoint being a six hour period free of seizures.<sup>37</sup> Both drugs were equally effective in controlling refractory SE (86% and 89% respectively), but higher seizure recurrence and mortality rates were seen with the infusion of midazolam. In a review article that included 54 adult SE patients, the use of a continuous IV midazolam infusion effectively treated 80% of adult SE patients, but was associated with a greater rate of breakthrough seizures than were the infusions of propofol and pentobarbital (51% vs. 15% and 12%, respectively).<sup>38</sup> The infusion of midazolam was, however, associated with less hypotension than were the other two infusions (30% vs 44% and 77%, respectively). Two other studies examined the use of a continuous IV midazolam infusion in adults, one with 33 patients<sup>38</sup> and one with seven patients whose outcome was compared to 13 treated with a propofol infusion.<sup>35</sup> In the study of 33 patients in non-convulsive SE, an infusion of IV midazolam was effective in treating 82% of patients.<sup>39</sup> In six patients treated with a midazolam infusion, the rate of seizure suppression was 67%.<sup>35</sup>

## **Conclusions:**

1. The use of continuous IV infusions of benzodiazepines is effective in treating 67-89% of SE patients.
2. In children, the use of a continuous IV diazepam infusion may be preferred over the use of a midazolam infusion, since it is associated with a lower rate of seizure recurrence and lower mortality.
3. In adults, the use of a continuous midazolam infusion is associated with a greater rate of breakthrough seizures than are propofol and pentobarbital, but it causes less hypotension than do the other two continuous infusions.

## **IV Pentobarbital:**

The use of a continuous IV infusion of pentobarbital has been studied in multiple adult case series.<sup>34,36,38</sup> When compared to the use of a IV infusion of propofol in 8 patients, pentobarbital was shown to be effective in terminating SE in 82% of patients, a rate higher than the 63% success rate seen with IV propofol.<sup>34</sup> The time to SE termination was, however, much longer with pentobarbital (123 vs. 3 minutes). In the 106 patients treated with IV pentobarbital in the Claassen review, pentobarbital had the highest treatment success rate (92%, as compared to 80% for IV midazolam and 73% for IV propofol).<sup>38</sup> Pentobarbital, however, was associated with the highest rate of hypotension requiring pressors as compared to propofol and midazolam (77% vs. 42% and 30%, respectively). In one of the studies summarized by Claassen, the outcome of 44 patients treated with IV pentobarbital was reviewed.<sup>36</sup> In this series, patient with significant toxic and metabolic derangements or anoxia as the cause of the refractory SE were least likely to

be effectively treated with IV pentobarbital, as compared to those with chronic epilepsy, infections, tumors, stroke, or trauma (91% vs. 29%, respectively).

**Conclusions:**

1. The infusion of IV pentobarbital is associated with the highest rate of successful adult SE treatment as compared to propofol and midazolam.
2. IV pentobarbital has a slower onset of action than does propofol, and is associated with a higher rate of hypotension requiring pressors than do propofol and midazolam.
3. IV pentobarbital was least successful in treating refractory SE in patient with significant toxic and metabolic derangements or cerebral anoxia.

## **Recommendations:**

### **Class A:**

In the treatment of seizures and SE, both the use of diazepam followed by a phenytoin or the use of lorazepam are acceptable acute treatment strategies, although lorazepam may be more effective in terminating SE.

### **Class B:**

In pediatric SE patients, IV lorazepam should be utilized rather than IV diazepam because of the greater risk of respiratory complications with IV diazepam use.

Phenobarbital is an effective alternative to the use of phenytoin in SE.

### **Class C:**

High dose phenytoin (up to 30 mg/kg) may be more effective in treating SE than standard doses.

Because it is water-soluble, fosphenytoin may be useful when safety concerns with the use of phenytoin exist.

The rapid infusion of IV valproate may be considered after benzodiazepines and phenytoins in the treatment of SE, or when hypotension is a potential concern.

IV benzodiazepine infusions are another option in the treatment of refractory SE. In children, the use of diazepam and midazolam infusion are equally effective, although IV midazolam infusions may be associated with higher breakthrough seizure and complication rates.

IV propofol and IV pentobarbital infusions may be considered in the treatment of refractory SE, noting that IV pentobarbital is associated with a high rate of hypotension requiring IV pressor support.

## References

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## **Patient Outcome**

The patient was initially treated with four doses of IV lorazepam, to a total dose of 8 mg. The patient continued to seize. The airway was patent with adequate vital signs and pulse oximetry readings. The patient was then treated with a rapid infusion of one gram fosphenytoin over 10 minutes, and then a second infusion of 500 mg of fosphenytoin over five minutes. The seizure activity then stopped. The patient was stable but unresponsive.

Cardiopulmonary, metabolic and toxicology tests were negative, as was a non-infused CT of the head. The initial levels of both phenytoin and Phenobarbital were found to be sub-therapeutic. An EEG was arranged for upon arrival to the ICU, and was completed within 90 minutes of the seizure onset. The patient was consulted by a neurologist, and was found not to be in subtle status epilepticus. The patient awoke within 12 hours and was discharged from the ICU the next day without any morbidity related to this prolonged seizure. The patient was discharged home with the instruction to take his medications as prescribed.

## Annotated Bibliography

### 1. Huff JS, Morris DL, Kothari RU, Gibbs MA. *Acad Emerg Med* 2001;8(6):622-8

This prospective study detailed the experience in twelve emergency departments over 5% of the calendar year. Seizures were noted in 1.2% of the 31,580 patients seen during that time period. The majority of patients were transported via EMS and received some type of diagnostic evaluation. Anti-epileptic drugs were given in 55% of patients. Half of the patients seized because of low anti-epileptic drug levels or complications of alcohol use.

### 2. Trieman. *N Engl J Med* 1998;12:792-798

This is a landmark study in that it attempted to define an optimal therapy in an emergency situation, status epilepticus (SE). This study, conducted mostly at VA hospitals, compared four accepted therapies in patients diagnosed with SE. This study defined successful therapy as the absence of clinical and EEG evidence of SE, an important design feature. Although lorazepam was shown to be superior to phenytoin, it was not shown to be superior to either phenobarbital or the combination of diazepam and phenytoin. There needs to be caution when generalizing these results to emergency department patients, since many of these patients were diagnosed as having subtle SE, often as a result of post-hypoxic encephalopathy. Also, the median seizure duration was nearly three hours, such that many of these patients were actually in refractory SE. Lastly, with the availability of IV fosphenytoin, all four of these therapies would likely have been comparable.

### 3. Leppik et al. *JAMA* 1983;249:1452-1454

This study was the first study to compare diazepam and lorazepam in the treatment of SE. These two therapies were found to be comparable in the treatment of GCSE but the data suggests that lorazepam might be superior in non-convulsive SE. Complication rates were comparable in the two treatment groups. The most important limitation of the study is the fact that the study may not have been adequately powered to detect a difference of less than 25% absolute between groups. Still, this study is a landmark study, using an excellent design given that day's standard.

### 4. Alldredge BK, Gelb AM, Isaacs SM, et al. *N Engl J Med* 2001;345:631-37

This study examined the outcome of 205 status epilepticus patients who were treated in the prehospital setting with either diazepam 5-10 mg, lorazepam 2-4 mg, or placebo. Patients treated with benzodiazepines were more likely to have the SE episode terminated prior to arrival than the placebo patients, and lorazepam was more effective than diazepam in terminating the SE episode (59% vs 43% vs 21% termination, respectively). Respiratory or circulatory complications were 10% in the actively treated patients, and 22% in those treated with placebo. This article is a must read for emergency physicians.

**5. Working Group on Status Epilepticus. *JAMA* 1993: 854-859**

This is an excellent summary article regarding the treatment of SE. It details the definition, epidemiology, and etiology of SE, and provides a consensus expert opinion regarding optimal diagnosis and therapy. There is also a minimal acceptable time course for the delivery of optimal therapies. This work group recommends having a clear plan for the treatment of SE. The use of drugs in optimal doses and the need for diagnostic testing that allows for metabolic changes to be optimally treated. This paper is the best overall article regarding principles for optimal SE management.

**6. Shaner DM, McCurdy SA, Herring MO, Gabor AJ. *Neurology* 1988;38:202-207**

This study compared the use of diazepam and phenytoin with the use of phenobarbital and optional phenytoin in 36 patients in SE. SE duration was noted to be shorter with the use of phenobarbital, and 61% of phenobarbital patients did not require the addition of phenytoin in order to terminate SE. Complication rates were comparable in the two treatment groups, suggesting phenobarbital as an alternative to the standard therapies including diazepam and phenytoin.

**7. Giroud M, Gras D, Escousse A, Dumas R, Venaud G. *Drug Investigation* 1993;5:154-9**

This is a pilot study from France that documents the outcome of 23 SE patients who were treated with IV valproate. Patients received a bolus infusion of 15 mg/kg followed by a six-hour infusion of 1 mg/kg/hr. Clinical SE was terminated in 83% of the 23 patients as was EEG evidence of subtle SE.

**8. Venkataraman V, Wheless JW. *Epilepsy Res* 1999;35:147-53**

This study documents the use of IV valproate in dosed up to 28 mg/kg at rates up to 6 mg/kg/minute in epilepsy patients as young as 2 years of age. The most rapid infusion rate in this study was 300 mg/minute. There were no significant BP or ECG changes noted in any of these patients as a result of these rapid valproate infusions.

**9. Stecker MM, Kramer TH, Raps EC, et al. *Epilepsia* 1998;39:18-26**

This study compared the use of a propofol infusion to high-dose barbiturate therapy in the management of 16 patients with SE. Although those treated with barbiturates were more likely to have the SE terminated (82% vs. 63%), SE termination occurred much faster with propofol (3 vs 123 minutes). In patients in whom the propofol infusion were quickly terminated, seizures were noted to recur, suggesting the need for slow termination of this AED therapy.

## Questions

- 1. All are true statements about status epilepticus (SE) except:**
  - a. It is defined by two seizures that occur without a lucid interval.
  - b. By definition, all SE is associated with generalized tonic-clonic motor activity.
  - c. Recent SE definitions include any seizure of duration > 10 minutes.
  - d. The most common etiologies for SE are low antiepileptic drug levels & alcohol withdrawal.
  - e. SE of longer duration is associated with a higher mortality.
  
- 2. All are true statements about status epilepticus (SE) except:**
  - a. By definition, subtle SE is not associated with generalized tonic-clonic motor activity.
  - b. Subtle SE requires EEG monitoring in order to be diagnosed clinically.
  - c. In subtle SE, the EEG shows persistent ictal discharges.
  - d. Because subtle SE does not have generalized tonic-clonic motor activity, it has a lower mortality rate than does GCSE.
  - e. Subtle SE occurs as a late finding of prolonged GCSE.
  
- 3. All are true statements about status epilepticus (SE) except:**
  - a. Fever can occur as a result of GCSE without the presence of a CNS infection as the fever source
  - b. Lumbar puncture is required for all SE patients who have a fever.
  - c. Lactic acidosis, leukocytosis, and hypercarbia can be in SE.
  - d. Guidelines exist that describe the role of neuroimaging in seizures and SE.
  - e. The diagnosis of refractory SE is made when initial therapies fail.
  
- 4. All are true statements regarding the use of EEG in SE except:**
  - a. Patients who remain comatose for > 30 minutes may be in subtle SE, requiring EEG monitoring.
  - b. All patients requiring neuromuscular blockage require EEG monitoring.
  - c. All patients requiring pentobarbital coma require EEG monitoring.
  - d. EEG monitoring can only be done with a multiple lead EEG machine.
  - e. In pts with subtle SE, EEG monitoring should be performed emergently in the ED or ICU.
  
- 5. All are true statements regarding the initial management of SE except:**
  - a. Lorazepam has been shown to be superior to other benzodiazepines in SE management.
  - b. Glucose determination, thiamine, and narcan are important initial therapies.
  - c. Most treatment failures relate to inadequate dosing, not drug therapy choice.
  - d. Phenytoins can be given in high doses (up to 30 mg/kg) in SE.
  - e. Propofol or phenobarbital can be used to treat SE after the benzodiazepines and phenytoins

- 6. If IV access is not available, the following are possible drugs and routes except:**
- a. IM midazolam
  - b. IM fosphenytoin
  - c. IM phenobarbital
  - d. PR diazepam
  - e. PR diazepam gel

**Answers**

**1. Answer: b.**

Although generalized convulsive SE (GCSE) is associated with tonic-clonic motor activity, other forms such as complex partial or absence SE can exist with this motor activity.

**2. Answer: d.**

Because subtle SE is a late finding of prolonged GCSE, it carries a much higher mortality than GCSE, up to 50-65% in some studies.

**3. Answer: b.**

Although a lumbar puncture should be considered in all patients with SE and fever, in the awake patient without meaningful signs and a fever source, an LP may not be necessary.

**4. Answer: d.**

Two channel EEG monitoring can be performed using the modular monitoring systems present in most EDs.

**5. Answer: a.**

No simple benzodiazepine has been shown to be superior to another for the treatment of SE.

**6. Answer: c.**

IM phenobarbital is not recommended because of soft tissue toxicity.