



## **What Do We Do When Benzodiazepines Fail?**

**Edward P. Sloan, MD, MPH, FACEP**

A 37-year old male is brought to the emergency department by EMS because of a seizure at home upon awakening. The patient had a generalized tonic-clonic seizure that lasted several minutes and spontaneously resolved, followed by a period of unresponsiveness during EMS transport. The patient is known to have a history of post-traumatic seizures that are managed with phenytoin and phenobarbital. The family stated that the patient has had neither recent illness nor head trauma. The family stated that they believed the patient was compliant with his medications, although non-compliance has been an issue in the past.

In the Emergency Department, the patient begins to respond to questions, but is still somewhat post-ictal. On initial exam, there are neither focal neurological findings nor any evidence of any other medical condition that would precipitate a seizure. The patient then has another generalized seizure with tonic-clonic seizure activity. The seizure lasts several minutes while medications were being obtained.

### **Key Learning Points**

1. There is good data to support the initial use of benzodiazepines in ED patients with seizures and SE. Both lorazepam and diazepam are useful IV agents, with slightly different characteristics that guide ED use.
2. The phenytoins are a useful second agent for use in ED SE patients. Factors such as the need for a rapid infusion, safety, the need for IM use, and cost will guide the ED physician in selecting fosphenytoin over phenytoin. Both may be useful in doses up to 30 mg/kg in SE patients.
3. Phenobarbital and valproate may be useful for the treatment of ED SE patients who are refractory to the benzodiazepines and phenytoins, as well as in pediatric patients.
4. Propofol can be utilized to achieve burst suppression in refractory SE patients, as can an IV midazolam infusion.

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**Epidemiology: What percent of ED patient present because of seizure disorders? What percent of ED seizure patients will not respond to initial treatment with benzodiazepines? Does efficacy differ between diazepam and lorazepam?**

**Conclusions:**

1. Up to 2% of all ED patients will present because 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 patients
5. Diazepam is expected to terminate seizures and SE in 43-76% of 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.

**Comments:**

There is reasonable data regarding the epidemiology of seizures in the ED. The data regarding which initial benzodiazepine suggests that lorazepam may be preferable in the most critically ill patients (those with prolonged SE) and in children. The use of lorazepam, however, may render the SE patient for a longer period of time, possibly requiring prolonged observation at a higher level of care. This may be important when considering the use of lorazepam as opposed to diazepam in ED SE patients.

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

**IV Phenytoins 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.

**Edward P. Sloan, MD, MPH, FACEP****Comments:**

Fosphenytoin may be useful in SE since it can be rapidly infused. It is intuitively obvious that fosphenytoin should be safer than phenytoin, since fosphenytoin is water-soluble and can be given IM when clinically indicated. Despite the publication of abstracts that suggest the greater safety of fosphenytoin, there have been no publications in the Emergency Medicine literature of these safety data. Once published, these fosphenytoin articles may allow for stronger recommendations to be made regarding its use in ED SE patients.

**IV Phenobarbital 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.

**Comments:**

Although phenobarbital is a useful drug in the treatment of SE, it is less often used because it must be given slowly in order to avoid respiratory depression. Despite this caveat, it is an effective drug that should be considered in any SE patient refractory to initial therapies.

**IV Valproate Conclusions:**

1. Valproate will control SE 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.

**Comments:**

IV valproate may be preferred over the phenytoins in ED patients with absence SE. It may also be useful in other SE patients, but there are no well-controlled US studies that confirm this potential use. Because it can be rapidly infused, it may be useful in SE patients after the use of the benzodiazepines and phenytoins. It also may be preferred over drugs such as phenobarbital or propofol because it has fewer cardiopulmonary effects than these drugs.

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**IV Propofol 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.

**Comments:**

Propofol is a drug that is used in the ED most often when intubation is required because of respiratory failure in otherwise relatively awake patients, such as in young status asthmaticus patients. It appears to provide burst suppression as does pentobarbital, but has fewer cardiopulmonary complications and can be utilized more easily in the ED. The studies suggest that an IV midazolam drip is another drug that should be considered when refractory SE is being treated.

**IV Midazolam Conclusions:**

1. Midazolam is comparable to diazepam at stopping refractory SE activity (86% and 89%, respectively), but higher seizure recurrence and mortality are seen over time with IV midazolam infusions.
2. Risks of breakthrough seizures are greater when using midazolam than with the use of IV propofol or IV pentobarbital.
3. The risk of hypotension is lower when using midazolam as compared to propofol or pentobarbital infusions.

**Comments:**

Higher rates of seizure recurrence or breakthrough seizures occur when an IV midazolam drip is used for the treatment of refractory SE rather than IV drips of diazepam, propofol or pentobarbital. These risks, however, must be balanced with the lower risk of hypotension seen in IV midazolam use, especially when compared to propofol or pentobarbital infusions.

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**Recommendations:**

**Class A:**

1. Treat patient who are actively seizing either with intravenous lorazepam or diazepam.

**Class B:**

None specified.

**Class C:**

1. In patients with refractory status epilepticus that do not respond to benzodiazepines, administer one of the following agents intravenously: high dose phenytoin, midazolam, pentobarbital, phenobarbital, propofol or valproic acid.

**Comments:**

Most of the recommendations that can be made regarding the treatment of SE in the ED are unfortunately Class C, since few randomized controlled trials have been conducted to support higher class recommendations. Because of the great deal of resources necessary to conduct a prehospital or ED study of SE, including the use of an exception to informed consent, it is not likely that higher level recommendations will be made based on new ED data. At best, a greater number of Class B recommendations may be made in the future as a result of publications of case series in the Neurology or Emergency Medicine literature.

**Case Management and Outcome**

The patient is initially treated with four doses of IV lorazepam, to a total dose of 8 mg, which is approximately 0.1 mg/kg. However, the patient continues to seize. The airway is patent with adequate vital signs and pulse oximetry readings. The patient is then given a rapid infusion of one gram of fosphenytoin over 10 minutes, and then receives a second infusion of 500 mg of fosphenytoin over five minutes. The generalized seizure then stops. The patient is stable but remains unresponsive for over 30 minutes in the ED while an ICU bed is being obtained.

Cardiopulmonary, metabolic and toxicology tests are negative, as is a non-infused CT of the head. The initial levels of both phenytoin and phenobarbital were found to be sub-therapeutic. An EEG is arranged for and is completed upon arrival to the ICU, within about 120 minutes of the seizure onset in the ED. The patient is consulted by a neurologist, and is found not to be in subtle status epilepticus based on the EEG result and neurologic exam. The patient awoke completely 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 two days later with the instructions to take his medications as prescribed, with neurology follow-up one week later.

**Diagnoses:**

1. Generalized convulsive status epilepticus due to AED non-compliance and sub-therapeutic drug levels.
2. Post-traumatic seizure disorder.