

Treating Emergency Department Seizure and Status Epilepticus Patients: Optimal Treatment Workshop

Non-IV Parenteral AEDs

1. List 5 anti-epileptic drugs (AEDs) that can be given intramuscular (IM) in an actively seizing patient.

1. Midazolam: 5 mg effective in minutes and is preferred IM AED
2. Lorazepam
3. Diazepam
4. Fosphenytoin: Therapeutic within 15-30 min
5. Phenobarbital...but this is not a preferred IM AED

2. Name 3 ways in which midazolam can be given through a non-IV parenteral route.

1. IM
2. Buccal
3. Intranasal

3. What is the most rapidly absorbed benzodiazepine when given through the intramuscular (IM) route?

Midazolam is the most rapidly absorbed benzodiazepine AED.

Non-IV Parenteral AEDs

4. Which parenteral AEDs should not be given through the intramuscular (IM) route?

Phenytoin should never be given IM, nor should large doses of phenobarbital be given IM.

5. What benzodiazepine preparation can be given through the per rectum (PR) route?

Diastat is a prepared emulsion of diazepam that can be given PR. It comes in 10 and 20 mg syringes and can be dosed in 2.5 mg increments.

6. What are the doses forms of the per rectum (PR) benzodiazepine preparations?

Diastat is dosed in 0.2 mg/kg to 0.5 mg/kg doses, with higher doses for younger aged children down to 2 years of age. 2-5 years old: 0.5 mg/kg; 6-11 years old: 0.3 mg/kg; 12 and older, 0.2 mg/kg.

7. What AEDs can be given via an endotracheal tube (ETT)?

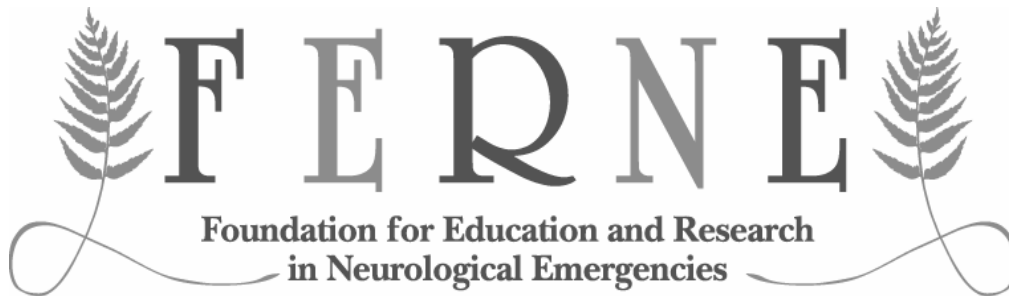
Practically speaking, the only AEDs that can or should be given via the ETT are the benzodiazepines, which are effective in small volumes. Otherwise, the IM or intraosseous route should be used.

8. What AEDs can be given intraosseously (IO)?

All of the AEDs that can be utilized via the IV route can also be given IO, including phenytoin.

9. Is there any rationale for AEDs to be given via an ETT or IO given other alternatives?

The initial use of an IM benzodiazepine, followed quickly by IM fosphenytoin makes the ETT or IO routes a secondary option in the actively seizing patient.



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Benzodiazepines

1. When comparing diazepam and lorazepam, which of these drugs has the more rapid time of onset?

Diazepam's onset is 1-5 minutes IV and 15-30 minutes IM. The onset of action for lorazepam is very similar. As such, clinically, the two drugs are very similar when utilized in treating ED seizure patients.

2. When comparing diazepam and lorazepam, which of these AEDs has the longer half-life and duration of action?

Although the peak effect of diazepam is in the range of 16-60 minutes, the peak effect of lorazepam can last for 6-12 hours, making it the preferred medication when recurrent seizures or status epilepticus is a concern.

3. What are the advantages and disadvantages to the use of diazepam in the treatment of actively seizing patients in the ED?

Because diazepam wears off relatively quickly, a single dose given to a patient with an isolated seizure will allow the patient to wake up relatively soon after the seizure. The patient, however, will be at risk for a recurrent seizure as the diazepam effect wears off over the first hour after the dose is given.

Benzodiazepines

4. What are the advantages and disadvantages to the use of lorazepam in the treatment of actively seizing patients in the ED?

Because lorazepam has an effect that last for hours, patients can remain obtunded, requiring observation to determine that the patient is appropriately waking up over time. The advantage of lorazepam is that its long duration of action means that recurrent seizures are less likely, as is prolonged SE. This makes this drug preferred in the most critically ill seizure and SE patients.

5. If diazepam is used in the treatment of seizing patients in the emergency department, what is the requirement for subsequent AED administration in order to prevent recurrent seizures from occurring?

Because diazepam wears off relatively quickly, the patient will be at risk for a recurrent seizure as the diazepam effect wears off over the first hour after the dose is given. As such, a longer acting AED such as phenytoin, phenobarbital or valproate must be provided if a recurrent seizure or SE is a concern.

6. What is the maximal dosage of diazepam that should be delivered prior to declaring that this benzodiazepine was not effective in the management of an actively seizing patient?

In the adult patient, unit doses of 5 mg IV diazepam can be given up to 4-5 times over 20 minutes. This is approximately 0.3 mg/kg IV in a 75 kg person. In pediatric patients, the dose is 0.2-0.5 mg/kg, a dose that can be repeated as in adults. (Example: A 20 kg child receives 4-5 mg per dose, similar to the dose in adults.)

7. What is the maximal dosage of lorazepam that should be delivered prior to declaring that this benzodiazepine was not effective in the management of an actively seizing patient?

In the adult patient, unit doses of 2 mg IV lorazepam can be given up to 5-6 times over 25 minutes. This is approximately 0.15 mg/kg IV in a 75 kg person. In pediatric patients, the dose is 0.05-0.1 mg/kg, a dose that can be repeated as in adults. (Example: A 20 kg child receives 1-2 mg per dose.)

Benzodiazepines

8. Which benzodiazepine is preferred in critically ill seizure and SE patients and why?

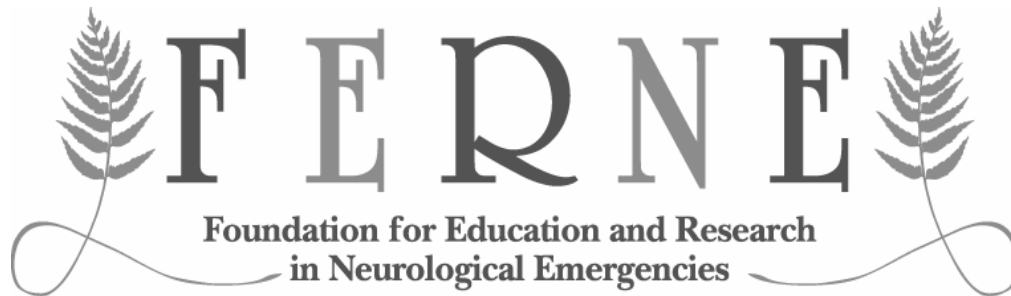
In every study that compares diazepam and lorazepam, there is a trend towards greater efficacy of lorazepam, especially in critically ill patients and those in SE. This, combined with the similar onset of action time and the longer duration of action make it the preferred benzodiazepine AED in these most ill seizure patients.

9. Which benzodiazepine is preferred in pediatric patients and why?

There are case reports and small case series that suggest that lorazepam can more effectively treat seizing pediatric patients with less risk of respiratory depression that would require airway support than with diazepam. Diazepam can, however, be used PR when IV access is not available.

Seizure Workshop Supported by Ortho-McNeil Neurologics, Inc.

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Phenytoins

1. What is the therapeutic range for the total phenytoin level, can this range be exceeded, and if so, why?

The therapeutic range for the total phenytoin level is 10-20 ucg/ml. This range was empirically chosen, and can be exceeded if it is deemed a higher phenytoin level is necessary to stop recurrent seizures or SE. When 30 mg/kg of a phenytoin are given, the total phenytoin level may go up to 30 ucg/ml.

2. What is the maximal acceptable phenytoin dose and infusion rate in an actively seizing SE patient?

A total dose of 30 mg/kg of a phenytoin can be given in order to maximize the antiepileptic effect of this AED. The maximum infusion rate for phenytoin itself is 50 mg/min. This is the appropriate rate for an actively seizing patient.

3. For every 1 mg/kg of a phenytoin infused, approximately how much does the total phenytoin level increase?

For every 1 mg/kg of a phenytoin infused, the total phenytoin level increases approximately 1 ucg/ml. A 10 mg/kg infusion will, therefore increase the total phenytoin level approximately 10 ucg/ml.

Phenytoins

4. What phenytoin rate was observed in the VA cooperative study of four AEDs patients in the treatment of SE patients?

In this study of 4 therapies for SE, the achieved infusion rate for phenytoin was only 30 mg/min. For a 75 kg person, this corresponds to less than 10 mg/kg over the 20 minute study period for SE termination. This means that the total phenytoin level would not achieve the 10 ucg/ml level during that time period, as so may not be achieve early SE termination.

5. What is the maximal infusion rate for fosphenytoin in SE patients?

The maximum infusion rate for fosphenytoin is 150 mg/min in phenytoin equivalents (PE). This is the appropriate rate for an actively seizing patient and those in SE.

6. Which therapy achieves a therapeutic free phenytoin faster: phenytoin at 50 mg/min or fosphenytoin at 150 mg/min, and at what time does this occur?

When phenytoin is infused at the maximum infusion rate of 50 mg/min and fosphenytoin is infused at 150 mg/min in phenytoin equivalents (PE), a therapeutic free phenytoin level of 1 ucg/ml is achieved at approximately the same time. This can be expected to occur at about 10-15 minutes after the infusion onset.

7. Is there a theoretical and/or proven outcome advantage to the use of fosphenytoin in the treatment of SE patients?

There is no proven benefit to the use of fosphenytoin in the treatment of actively seizing patients and those in SE. Theoretically, if the infusion of fosphenytoin takes place more quickly, it is possible logistically to plan for the infusion of the next AED instead of waiting the longer period of time for the phenytoin infusion to be completed. (One gram of phenytoin takes 20 minutes to infuse, one gram fosphenytoin PE takes less than 7 minutes to infuse.)

Phenytoins

8. What is the maximum IM fosphenytoin volume that can be given in a single injection site, and how many mg of phenytoin can be provided with this maximal IM volume?

The maximum IM injection volume of fosphenytoin studied is 20 cc in a single injection site. This corresponds to 1 gram of fosphenytoin in phenytoin equivalents (PE). The fosphenytoin concentration is 50 mg/ml. The phenytoin level is therapeutic within 15-30 minutes following IM use.

9. What are the requirements regarding obtaining a total phenytoin level following the use of IM or IV fosphenytoin, and why?

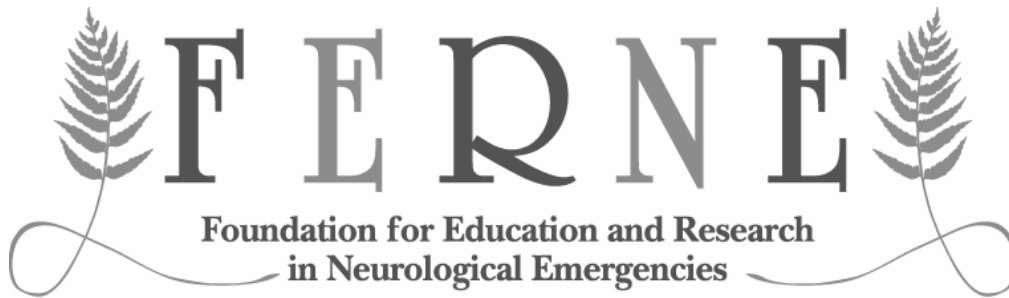
Because there is a cross-reactivity of the fosphenytoin molecule in the phenytoin assay, it is necessary to wait two hours after an IV infusion of fosphenytoin and four hours after an IM fosphenytoin injection before obtaining a serum phenytoin level. If done earlier than these time periods, a falsely elevated phenytoin level may be observed.

10. Are the pruritus and paresthesias that can occur when administering fosphenytoin a histamine mediated allergic reaction, and how should these symptoms be treated?

The pruritus and paresthesias that can occur (especially in the groin) when administering fosphenytoin are NOT histamine mediated allergic reactions. They cannot be mitigated by pre-treatment with steroids or treated with anti-histamines such as diphenhydramine. Instead, simply turn the infusion rate down to one-half the current rate and these symptoms should resolve over several minutes.

11. What is the most commonly observed important adverse effect when providing fosphenytoin at its maximal infusion rate, especially in older SE patients?

When infusing fosphenytoin at its maximal infusion rate of 150 mg/min PE, especially in older SE patients, hypotension can occur. This adverse effect can be treated effectively by turning down the infusion rate or stopping it altogether. Infusions of normal saline can be provided in order to restore an adequate BP in most cases.



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Levetiracetam

1. What is the therapeutic range for the total levetiracetam level, and can this range be exceeded?

Although epileptologists may follow a levetiracetam level in individual patients over time, there is no broadly used therapeutic levetiracetam level clinically. Decisions must be made based on the current dose, medication compliance, and the occurrence of seizures.

2. What is the maximal acceptable levetiracetam dose and infusion rate in an actively seizing SE patient?

Doses of IV levetiracetam ranging from 1500 to 4000 mg have been studied, and these doses have been infused in 5 to 15 minutes without complication in seizure patients. Levetiracetam infusions such as these have not been studied, however, in actively seizing patients or those in SE.

3. For every 1 mg/kg of a levetiracetam infused, approximately how much does the total levetiracetam level increase?

Because there is no clinically useful levetiracetam level, this type of calculation is not used to determine an IV dose in ED seizure patients.

4. How do the kinetics and bioavailability of IV levetiracetam compare to PO levetiracetam?

IV and PO levetiracetam are bioequivalent. You would, therefore, use these agents in a similar fashion, unless the PO route is not an option, in which case IV levetiracetam is preferred.

Levetiracetam

5. If you wish to load a non-seizing ED patient with levetiracetam, what is the usual dose range?

When loading an ED seizure patient with levetiracetam, the normal loading dose range is 500-1500 mg, regardless if the loading dose is being provided PO or IV.

6. What is the usual levetiracetam daily starting dose in patients who have not taken this AED previously?

The normal starting daily dose is 500 mg BID, and this amount can be increased by 1000 mg per day every two weeks to a maximum daily dose of 3000 mg per day.

7. Since levetiracetam levels cannot commonly be obtained in clinical practice, how should adjustments in daily levetiracetam dosing be made in medication compliant break-through seizure patients?

In general, it is possible to increase the daily levetiracetam dose by 1000 mg per day (500 mg BID) up to the maximum daily dose. (Example: ED pt on 500 mg BID has breakthrough seizures: send home on 1000 mg BID and notify PMD of this change.)

8. How do the second generation AEDs compare to the first generation AEDs with regard to safety, efficacy, and tolerability?

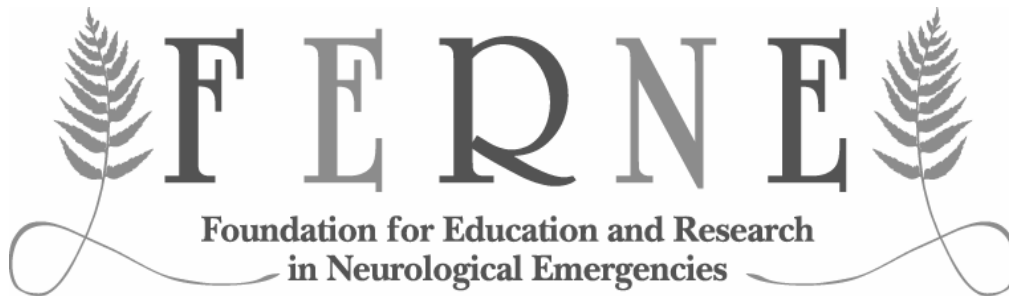
In general, second generation AEDs are comparable to first generation AEDs with regard to safety and efficacy. These newer AEDs are, however, better tolerated by patients, theoretically leading to better compliance and clinical effectiveness.

9. In what patients might this AED be optimal, given its pharmacologic properties?

Because levetiracetam is renally excreted, this AED may be preferred in patients who have liver disease, failure, or a hepatic transplant. It might also be preferred due to the lack of drug-drug interactions with phenytoin, valproate, digoxin, warfarin, probenecid, and oral BCPs.

10. What are the commonly observed adverse effects that are observed with patients who are started on levetiracetam?

In clinical trials, the most common adverse effects of IV levetiracetam are somnolence, asthenia, headache, infection, and dizziness. Some patients also experience behavior abnormalities such as emotional lability during the first four weeks of levetiracetam therapy.



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Valproate

- 1. What is the therapeutic range for the valproate level, and can this range be exceeded?**

The therapeutic range for a serum valproate level is approximately 40 to 125 ucg/ml. This range can be exceeded safely in ED patients who are experiencing a flurry of seizures and in SE patients.

- 2. What is the maximal acceptable valproate dose and infusion rate in an actively seizing SE patient?**

The maximum valproate infusion rate that can be safely utilized in adult seizure patients is 300 mg/min. In children, the maximum valproate infusion rate is 6 mg/kg/min in doses up to 15 mg/kg.

- 3. For every 1 mg/kg of a valproate infused, approximately how much does the valproate level increase?**

For every 1 mg/kg of a valproate infused, the valproate level increases approximately 5 ucg/ml. (Example: An infusion of 20 mg/kg will increase the valproate level approximately 100 ucg/ml.)

Valproate

4. What are the common adverse effects observed when infusing IV valproate at this maximal rate in an SE patient?

The most commonly observed adverse events notes during these rapid IV valproate infusions were dizziness, somnolence, and site pain. These were resolved successfully with changes in the infusion rate. There were no significant BP or HR changes noted.

5. If an actively seizing ED patient is thought to be compliant with PO Depakote and requires the administration of an IV valproate loading dose, can it be provided without first obtaining a serum valproate level? If so, how and why?

Because the serum valproate level can safely exceed the therapeutic level range, it is possible to half load an actively seizing ED patient who takes PO Depakote without verifying the level first. (Example: Baseline level is 96 ucg/ml, half load of 10 mg/kg given IV, new valproate level after infusion is 146 ucg/ml.)

6. Should IV valproate be provided in an actively seizing patient who takes PO Depakote prior to administering a benzodiazepine or a phenytoin?

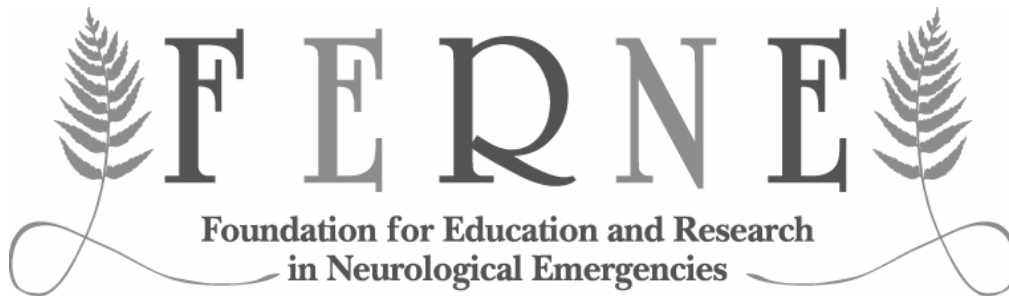
As is true with all actively seizing ED patients, the first therapy to be provided is a benzodiazepine. However, for patients who take oral Depakote, an infusion of IV valproate should be considered for administration prior to infusing an IV phenytoin.

7. What is the common clinical presentation for Juvenile Myoclonic Epilepsy, and why is a valproate load perhaps optimal in ED seizure patients with this presumed diagnosis?

JME is a diagnosis made in college-aged patients who have a history of myoclonic jerks and have a generalized seizure after prolonged sleeplessness and/or binge alcohol drinking. A valproate load may be preferred because it is associated with fewer seizures than is a regimen of IV loading and oral phenytoin.

8. In what patients should IV valproate be avoided, and why?

Valproate should be avoided in patients who are pregnant or who are attempting to become pregnant. It should also be avoided in patients with significant liver or pancreatic disease, and in children less than 2 years of age, in whom complications can occur more commonly.



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Continuous Infusion AEDs

1. What are the advantages and disadvantages for the use of midazolam as a continuous infusion AED in the treatment of refractory SE patients?

A continuous infusion of midazolam is a useful option because it utilizes a benzodiazepine that is commonly utilized via intermittent bolus in the ED. A continuous midazolam infusion, however, is not commonly used in ED clinical practice, and SE refractory to this infusion is more common than with the continuous infusion of propofol or pentobarbital.

2. How should midazolam be bolused, infused and titrated when treating actively seizing SE patients?

Midazolam can be bolused at 0.05 mg/kg and then infused at 0.03 mg/kg/hr, up to 5 mg per hour continuous infusion. (Example: 80 kg adult receives a bolus of 4 mg, then a continuous infusion of 2.4 mg per hour, titrated up to 5 mg per hour as needed.)

3. What are the advantages and disadvantages for the use of propofol as a continuous infusion AED in the treatment of refractory SE patients?

A continuous infusion of propofol is a useful option because it is a therapy that is already commonly utilized in the ED when managing mechanically ventilated patients. It also can be reversed quickly when a subsequent neurological exam is desired. Hypotension can be observed more commonly with a continuous propofol infusion than with a midazolam infusion.

Continuous Infusion AEDs

4. How should propofol be bolused, infused and titrated when treating actively seizing SE patients?

Propofol can be bolused at 0.25 mg/kg, then infused at 0.6 mg/kg/hr. (Example: 80 kg adult receives a bolus of 20 mg, then a continuous infusion of 48 mg per hour, titrated higher every five minutes as needed to adequate sedation, provide adequate SE burst suppression.

5. What are the advantages and disadvantages for the use of pentobarbital as a continuous infusion AED in the treatment of refractory SE patients?

In general, a pentobarbital coma is a therapeutic approach that is implemented only in the ICU and with continuous EEG monitoring under the direction of a neurologist or epileptologist.

6. What are the complications of these continuous infusion AEDs when treating SE patients?

The most commonly observed complications of these continuous infusions are lack of effectiveness in terminating SE, significant hypotension, tachyphylaxis, and increased mortality.

7. What is the recommendation of some epileptologists regarding the use of intermittent bolus and continuous infusion AEDs when treating actively seizing SE patients in the ED?

Because prolonged SE is a highly lethal disease, some epileptologists believe that any SE patient who does not respond to maximal doses of a benzodiazepine and a phenytoin should immediately be started next on a continuous infusion AED.

8. What recommendations are made regarding EEG monitoring in the treatment of actively seizing SE patient who requires a continuous AED infusion?

Because continuous AED infusion is provided to terminate SE, including subtle SE, it is important to know that SE has been terminated by providing continuous EEG monitoring. ED patients started on a continuous midazolam or propofol infusion should receive continuous EEG monitoring upon arrival to the ICU.