



First Line Therapy in Acute Seizure Management

William C. Dalsey, MD, MBA, FACEP

A 32-year old male intravenous drug user was brought to the ED having had a witnessed generalized tonic-clonic seizure 10 minutes prior to presentation. The patient arrived post-ictal but responsive. No other medical history was available. On exam the blood pressure was 130/80 mm Hg, heart rate 88, respirations 14, and oxygen saturation of 98% on room air. The head was atraumatic, the pupils were 4 mm and reactive, cardiopulmonary exam was normal. Neurologically, the patient was oriented to person only; had no facial asymmetry, moved all four extremities, deep tendon reflexes were +4 symmetrically and no Babinski reflexes were present. A stat blood sugar was 110 mg/dl. While looking for venous access over the patient's scarred extremities the patient began a second generalized tonic clonic seizure.

Questions:

1. What is the “best” first line therapy for acute seizure management?
2. What options are available when intravenous access is not available?
3. What are the role of rectal benzodiazepines and intramuscular fosphenytoin?

Key Learning Points:

1. Use a benzodiazepine as the first-line therapy.
2. If there is no IV access consider IM versed or posphenytoin, or rectal valium.
3. Lorazepam is the preferred first line agent for seizure control due to its long lasting anticonvulsant properties.
4. Diazepam is equally effective but requires that a concomitant, long acting AED be administered (ie Dilantin).
5. When the IV access is unavailable, alternate routes such as IM injections of midazolam, rectal solutions of diazepam, and IM fosphenytoin should be considered; of the three, IM midazolam is probably the fastest and easiest to use.

What is the best first line therapy for acute seizure management?

Benzodiazepines are considered the best first line drugs in managing status epilepticus and have been shown to be equal or superior to phenobarbital alone and superior to using phenytoin alone. (Treiman 1989) Treiman reviewed 47 clinical studies involving 1346 patients treated with either diazepam, lorazepam, or clonazepam. (Treiman 1989) A composite seizure control rate of 79% was reported without one benzodiazepine demonstrating superiority in seizure control over another.

Diazepam, 0.2 mg/kg at 5 mg/min, and lorazepam, 0.1 mg/kg at 2 mg/min are equally effective in terminating seizures however lorazepam has the advantage of a much smaller volume of distribution. Lorazepam's small volume of distribution results in anticonvulsant activity that lasts up to 12 hours versus 20 minutes for diazepam that rapidly redistributes in lipid stores throughout the body (Treiman 1988). Diazepam's short duration of action places the patient at risk for seizure recurrence unless a longer acting AED is administered. Prenskey et al reported that only nine of 20 patients treated with diazepam remained seizure free two hours after treatment (Prenskey); while in another study, only 16% of patients treated with lorazepam had a recurrent seizure in twenty four hours (Treiman). When diazepam is used as the initial AED, intravenous phenytoin loading, 18-20 mg/kg, should also be started to prevent recurrent seizures.

In a randomized double blind study by Treiman et al, lorazepam was recommended as the best first line AED because of its efficacy and its ease of administration. An additional advantage of lorazepam may be that it is associated in a few studies with a slightly lower incidence of respiratory depression than diazepam. In a retrospective review by Chiulli et al, intravenous lorazepam was associated with a 37% incidence of intubation compared to 73% with diazepam; however, this finding needs confirmation with a prospective study. (Chiulli) Other studies have demonstrated no significant difference in adverse events between the two benzodiazepines. (Leppik)

What options are available when intravenous access is not available?

When intravenous access is unattainable, rectal, IM, and intraosseous routes have all been used to administer antiepileptic medications. In the ED, each route has certain advantages and disadvantages. Optimal drugs for intramuscular delivery are water soluble with a neutral pH. For example, phenytoin cannot be given intramuscularly because its alkaline pH will result in significant tissue necrosis. Optimal drugs for rectal delivery are lipid-soluble and non-ionized, with solutions providing faster results than suppositories. Drugs are absorbed passively through lipid membranes. Although some drugs may have a cathartic effect, the advantage of rectal administration is that the route bypasses the portal circulation and first-pass hepatic elimination. (Woody)

Intramuscular or intranasal midazolam is an excellent option when intravenous access is not available since it is water soluble, nonirritating, and rapidly absorbed. (Orebaugh, Kendall, Chamberlain) In a study by Jawad and colleagues, (Jawad) intramuscular midazolam was

effective as quickly as IV diazepam. Midazolam, 10 to 15 mg, given intramuscularly reduced the mean number of spikes on an EEG within 5 to 15 minutes, similar to an intravenous administration of diazepam (10 or 20 mg). Kendall reported two cases of status epilepticus, one in a 2 year old child and one in an adult, that were successfully terminated with intranasal midazolam, 1.6 mg and 10 mg respectively. (Kendall) Midazolam may also be used buccally (10 mg dose for children over the age of 5 years), and nasally, with a recommend dose of 0.2 mg/kg. (Richens)

Diazepam may be administered intravenously or rectally. Intramuscular diazepam is not absorbed consistently. In a study by Moolenaar and colleagues (Moolenaar), 10 adult volunteers were given a 10-mg dose of diazepam by various routes, with maximum serum concentrations (C_{max}) and the time to peak serum concentration (T_{max}) measured and averaged between individuals. Intravenous diazepam reached its maximum serum concentration in 6 minutes. A rectal solution of diazepam had a time to peak serum concentration of 17 minutes. Orally administered diazepam had a T_{max} of 52 minutes, rectal suppositories took 82 minutes, and intramuscularly administered diazepam took 95 minutes to attain maximum serum concentrations. Of note, anticonvulsant efforts usually begin before C_{max} is reached.

Studies in young children suggest that a single rectal dose of 0.5 mg/kg diazepam solution provides effective anticonvulsant levels of AED in 3 minutes. (Dooley, Kriel) In a prehospital study, Dieckmann reported that 13 of 16 children who received rectal diazepam stopped seizing after a single dose; seizures recurred in 4 of the children before ED arrival. (Dieckmann) None of the children suffered complications from the rectal diazepam. Unfortunately there was no control group to ascertain whether it was the diazepam or the natural course of the seizures that resulted in termination. Children with serial seizures had fewer seizures over time when given diazepam solution versus placebo. (Kriel, Cereghino) In a double blind placebo controlled study, rectal diazepam gel was reported to significantly reduce the median seizure frequency in children predisposed to repetitive seizure. (Cereghino). The most frequently reported complication was somnolence. Rectal doses of diazepam solution range from 0.5 mg/kg for children between the ages of 2 and 5 years of age, 0.3mg/kg for children between the ages of 6 and 11 years of age, and 0.2 mg/kg for children of 12 years of age and older. Prepackaged commercial syringes with adult and pediatric-sized tips are available in doses of 2.5, 5, 10, and 20 mg. Multiple syringes may be used; for instance, a child needing a 7.5 mg dose would receive a 2.5- and a 5-mg dose.

Fosphenytoin, a phosphate ester of phenytoin, became available in 1995 and has a safety profile that makes it preferable to phenytoin in certain situations. Fosphenytoin is water soluble obviating the need for the propylene glycol vehicle. It can be given intramuscularly or intravenously with 100% bioavailability. Fosphenytoin is less of a tissue irritant than the phenytoin/propylene glycol preparation, with pruritis and paresthesias the most common side effects. There are minimal cardiotoxic effects though hypotension has been reported with rapid intravenous infusions. (Leppik) Blood pressure should be carefully monitored, especially in patients with underlying cardiovascular disease, when given intravenously, while monitoring is not necessary when it is given intramuscularly. While fosphenytoin works fastest when given intravenously, it is well absorbed by the IM route with 100% bioavailability. It should reach therapeutic serum levels within one hour of administration though its therapeutic benefit may be

seen much earlier. Other standard AEDs given orally or rectally, such as valproic acid or carbamazepine, take too long to achieve therapeutic serum levels and thus are inappropriate for emergency use.

Conclusions

1. Use a benzodiazepine as the first-line therapy.
2. If there is no IV access consider IM versed or Fosphenytoin, or rectal valium.

Seizure management in the ED requires a risk benefit analysis that balances the patient's needs with the urgency of the situation. Lorazepam is the preferred first line agent for seizure control due to its long lasting anticonvulsant properties. Diazepam is equally effective but requires that a concomitant, long acting AED be administered (ie Dilantin). When the IV access is unavailable, alternate routes such as IM injections of midazolam, rectal solutions of diazepam, and IM fosphenytoin should be considered; of the three, IM midazolam is probably the fastest and easiest to use.

Other Information in the Literature

Alternative agents for therapy include valproate, lidocaine and propofol. Lidocaine can be administered via the ETT as can valium. Valium may cause pneumonitis. The definition of Status Epilepticus can vary from 5, to 20 to 30 minutes. The most commonly misunderstood aspect of status is that the patient must return to his baseline to not be in status. Though brain damage is theoretically possible and may occur with brief seizures, significant brain injury is unlikely unless a patient has prolonged seizures. Brain injury and refractory status can occur from hypoxia and hypoglycemia so these must be avoided. In refractory status each subsequent AED provides only modestly greater effect on seizure cessation. Very large doses of medications may be necessary to stop refractory status epilepticus.

There are insufficient prospective randomized clinical trials to determine the best treatments for status, prevention of brain injury, recurrent seizure and minimizing complications to provide the best overall outcomes.

Reference List

1. Cereghino J, Mitchell W, Murphy J, et al. Treating repetitive seizures with a rectal diazepam formulation. *Neurology* 1998; 51:1274-1282.
2. Chamberlain J, Altieri M, Futterman C, et al. A prospective randomized study comparing intramuscular midazolam with intravenous diazepam for the treatment of seizures in children. *Pediatr Emerg Care* 1997; 13:92-94. (Controlled clinical trial, 24 patients)
3. Chiulli D, Terndrup T, Kanter R. The influence of diazepam or lorazepam on the frequency of endotracheal intubation in childhood status epilepticus. *J Emerg Med* 1991; 9:13-17.
4. Cloyd JC, Kriel RL. Bioavailability of rectally administered valproic acid syrup. *Neurology*. 1981;31:1348-52.
5. Cranford R, Leppik I, Patrick B, et al. Intravenous phenytoin: Clinical and pharmacokinetic aspects. *Neurology* 1978; 28:874-880. (Prospective pharmacokinetic observational study, 139 patients)
6. Dieckmann R. Rectal diazepam for prehospital pediatric status epilepticus. *Ann Emerg Med* 1994; 23:216-224.
7. Dooley JM. Rectal use of benzodiazepines. *Epilepsia*. 1998;39:S24-27.
8. Dulac O, Aicardi J, Rey E, Olive G. Blood levels of diazepam after single rectal administration in infants and children. *J Pediatr*. 1978;93:1039-41.
9. Jawad S, Oxley J, Wilson J, Richens A. A pharmacodynamic evaluation of midazolam as an antiepileptic compound. *J Neurol Neurosurg Psychiatry*. 1986;49:1050-4.
10. Kendall J, Reynolds M, Goldberg R. Intranasal midazolam in patients with status epilepticus. *Ann Emerg Med* 1997; 29:415-417.
11. Kriel RL, Cloyd JC, Hadsall RS, Carlson AM, Floren KL, Jones-Saete CM. Home use of rectal diazepam for cluster and prolonged seizures: efficacy, adverse reactions, quality of life, and cost analysis. *Pediatr Neurol*. 1991;7:13-7.
12. Leppik I, Derivan A, Homan R, et al. Double-blind study of lorazepam and diazepam in status epilepticus. *JAMA* 1983; 249:1452-1454.
13. Leppik I, Boucher R, Wilder B, et al. Phenytoin prodrug: Preclinical and clinical studies. *Epilepsia* 1989 (suppl 2); 30:S22-S26.

14. Moolenaar F, Bakker S, Visser J, Huizinga T. Biopharmaceutics of rectal administration of drugs in man IX: Comparative biopharmaceutics of diazepam after a single rectal, oral, intramuscular, and intravenous administration in man. *Int J Pharmaceut.* 1980;5:127-137.
15. Orebaugh S, Bradford S. Intravenous versus intramuscular midazolam in treatment of chemically induced generalized seizures in swine. *Am J Emerg Med* 1994; 12:284-287.
16. Prensky A, Raff M, Moor M, et al. Intravenous diazepam in the treatment of prolonged seizure activity. *New Engl J Med* 1967; 276:779-784.
17. Treiman D, DeGiorgio C, Ben-Menachem E, et al. Lorazepam versus phenytoin in the treatment of generalized convulsive status epilepticus. *Neurology* 1985; 35:284
18. Treiman D. Pharmacokinetics and clinical use of benzodiazepines in the management of status epilepticus. *Epilepsia* 1989;30:S4-S10.
19. Treiman D, Pharmacokinetics and clinical use of benzodiazepines in the management of status epilepticus. *Epilepsia* 1989; 30:4-10.
20. Treiman D, Meyers P, Walton N, et al. A comparison of four treatments for generalized convulsive status epilepticus. *New Engl J Med* 1998; 339; 792-798.
21. Woody RC, Laney SM. Rectal anticonvulsants in pediatric practice. *Pediatr Emerg Care.* 1988;4:112-6.

Annotated Bibliography

- 1.) Cereghino J, Mitchell W, Murphy J, et al. Treating repetitive seizures with a rectal diazepam formulation. Neurology 1998; 51:1274-1282.**

This study, in addition to a similar study in the New England Journal published the same year, supports the home administration of rectal diazepam gel to children at risk for acute repetitive seizures. The study's double blind placebo controlled design demonstrated that rectal diazepam gel is better than placebo is terminating seizures and preventing recurrence. It also demonstrated that care givers at home could safely administer the prepackaged rectal gel.

- 2.) Dieckmann R. Rectal diazepam for prehospital pediatric status epilepticus. Ann Emerg Med 1994; 23:216-224.**

Retrospective analysis of 324 patients who were less than 18-years of age with seizure. Of 36 patients in status epilepticus, 18 received rectal diazepam and 15 intravenous diazepam. 81% of the children receiving rectal diazepam stopped seizing though seizures reoccurred in 30% prior to hospital admission. All of the children who received intravenous diazepam stopped seizing however 60% had a recurrent event. The study suggests that rectal diazepam is effective and may be better at preventing recurrence of seizures than intravenous diazepam. The study was not blinded and suffers from possible selection bias and a small number of patients.

- 3.) Flomembaum N (ed). Treating acute seizure patients in the emergency department. Emerg Med 1996;(suppl):1-32.**

This supplement is dedicated to acute seizure management with a focus on fosphenytoin. Included are articles on the pharmacokinetics and administration of fosphenytoin, and on IM administration of fosphenytoin

- 4.) Leppik I, Derivan A, Homan R, et al. Double-blind study of lorazepam and diazepam in status epilepticus. JAMA 1983; 249:1452-1454.**

A double blind, randomized study involving 78 patients comparing 4 mg of lorazepam to 10 mg of diazepam. Lorazepam controlled 89% of seizures while diazepam controlled 76%. Time to onset and adverse outcomes did not differ between the two benzodiazepines.

- 5.) Treiman D. The role of benzodiazepines in the management of status epilepticus. Neurology 1990; 40:suppl2):32-42.**

This is an excellent review article that discusses mechanism of action, pharmacokinetics, indications and complications of the benzodiazepines.

6.) Treiman D, Meyers P, Walton N, et al. A comparison of four treatments for generalized convulsive status epilepticus. *New Engl J Med* 1998; 339; 792-798.

This is an important study that compared the efficacy of lorazepam, diazepam plus phenytoin, phenytoin, and Phenobarbital as first line treatments for status epilepticus. 384 patients were enrolled and outcomes were measured at 12 hours and 30 days. There was no difference among the treatment with respect to recurrence or adverse reactions. Lorazepam was recommended as the first line therapy because of its equal efficacy and ease of use.