REFRACTORY STATUS EPILEPTICUS
NEW DRUGS AND CHALLENGES

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The First Hour Belongs to us

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Learning objectives

- Update on current definition of SE and RSE
- Mortality
- Management Priorities for SE and RSE
- Drug Regimens for RSE

10 yr old with history of epilepsy presents with 10 minute history of generalized tonic clonic activity. Pt received Midazolam by Paramedics and on arrival to hospital continues to seize ?

Your thoughts ?

Definition of SE

Continuous seizures lasting at least 5 minutes or two or more discrete seizures between which there is incomplete recovery of consciousness

- Millikan D -*Emergency Treatment of Status Epilepticus: Current Thinking* Emerg Med Clin North Am - 01-FEB-2009; 27(1): 101-13, ix

Our Case

10 yr old with history of epilepsy presents with 10 minute history of generalized tonic clonic activity. Pt received Midazolam by Paramedics and on arrival to hospital continues to seize ?

Benzodiazepine given

Phenytoin or Fosphenytoin

Continues to have SEIZURE ????

Refractory Status Epilepticus

- Failure to respond to sequential treatment to benzodiazepine and phenytoin (one AED)
- Duration of Seizure after initiation of treatment is no longer a consideration

- Gretchen et al. Guidelines for the Evaluation and Management of Status Epilepticus. NeuroCritical Care April 2012
- Abend NS -Treatment of Refractory Status Epilepticus: Literature Review and a Proposed Protocol *Pediatr Neurol* - 01-JUN-2008; 38(6): 377-90


SPEED
KILLS

In ED

Mortality

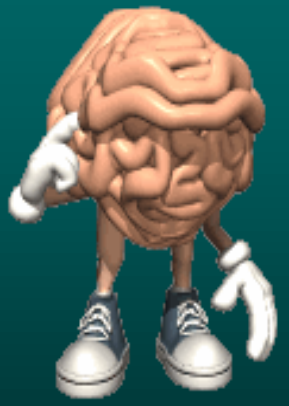
- Infants 29%
- Children 2-3%
- Adults 20-30%
- Duration of SE
  - < 1 hr 2.7 %
  - > 1 hr 32 %

- Respall-Chaure M. et al: The epidemiology of convulsive status epilepticus in children: a critical review. *Epilepsia* 48. 1652-1663.2007;

Seizure ?

Management Refractory Status Epilepticus

To control seizure activity URGENTLY



Management

ABC, Oxygen
Monitor Vital Signs
Blood Glucose

↓

Glucose

↓

Start ACT

↙ ↘

Focused Hx, P/E

Investigations

Management

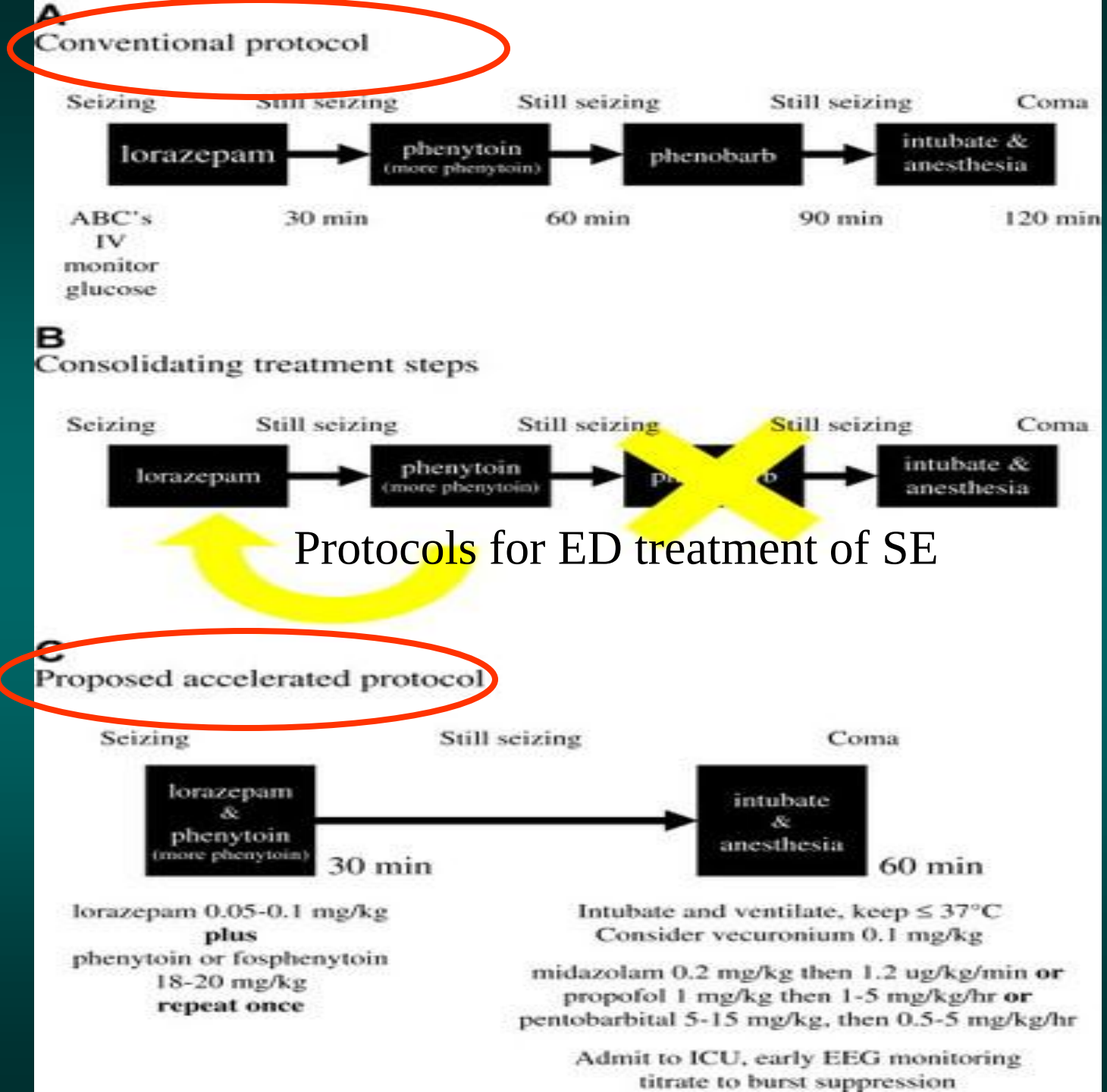
- Benzodiazepine and one additional AED
- Drugs: Antiepileptic drugs (AEDs)
  - Common errors
    - Delay in treatment initiation
    - Under dosing medication
    - Excessive intervals between medications
    - Inappropriate medication choices and routes of administration

- SEIZURE CONTINUES

Protocols for ED Treatment of RSE

Millikan D -*Emergency Treatment of Status Epilepticus: Current Thinking* Emerg Med Clin North Am - 01-FEB-2009; 27(1): 101-13, ix

Shearer P - *Emerg Med Clin North Am* - 01-FEB-2011; 29(1): 51-64


A
Conventional protocol
Seizing
Still seizing
Still seizing
Still seizing
Coma
lorazepam
phenytoin
(more phenytoin)
phenobarb
intubate &
anesthesia
ABC's
IV
monitor
glucose
30 min
60 min
90 min
120 min
B
Consolidating treatment steps
Seizing
Still seizing
Still seizing
Still seizing
Coma
lorazepam
phenytoin
(more phenytoin)
intubate &
anesthesia
Protocols for ED treatment of SE
C
Proposed accelerated protocol
Seizing
Still seizing
Coma
lorazepam
&
phenytoin
(more phenytoin)
30 min
intubate
&
anesthesia
60 min
lorazepam 0.05-0.1 mg/kg
plus
phenytoin or fosphenytoin
18-20 mg/kg
repeat once
Intubate and ventilate, keep ≤ 37°C
Consider vecuronium 0.1 mg/kg
midazolam 0.2 mg/kg then 1.2 ug/kg/min or
propofol 1 mg/kg then 1-5 mg/kg/hr or
pentobarbital 5-15 mg/kg, then 0.5-5 mg/kg/hr
Admit to ICU, early EEG monitoring
titrate to burst suppression

Veterans Affairs Status Epilepticus **Cooperative Study**

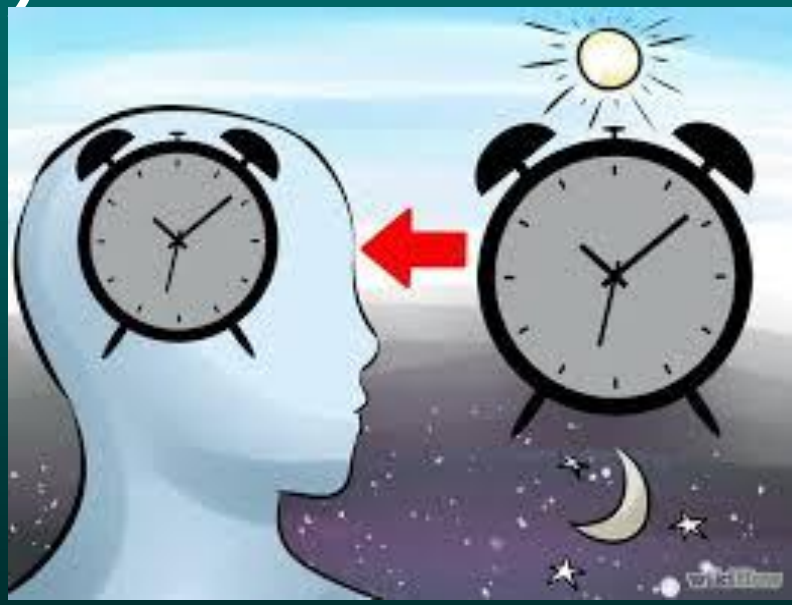
- RCT
- Compared four distinct treatments for SE in subjects with a variety of seizure types
- Intravenous lorazepam at 0.1 mg/kg effective and easier to use than alternative treatments, including phenobarbital, diazepam plus phenytoin, and phenytoin
- Patients who failed 1st line, addition of a 2nd & 3rd drug increased success chances by 5% and 2.3%
- Sequential approach time consuming and delayed effective seizure control

Accelerated drug delivery

Time To Treatment

30 minutes

- 86% vs.15% (children)
- 80% vs. 40% (adults)
  - Lewena et al EM Australia 2006
  - Holtkamp et al. J Neurology 2005



e

Refractory Status Epilepticus

- Gretchen et al. Guidelines for the Evaluation and Management of Status Epilepticus. NeuroCritical Care April 2013

Midazolam	**Class IIa, level B**
Valproate Sodium	Class IIa, Level B
Propofol	Class IIb, Level B
Keppra	Class IIb, Level C

Refractory Status Epilepticus

- Midazolam
  - Meta-analysis of five drugs (diazepam, isoflurane, **midazolam**, pentobarbital, and thiopental)
  - Efficacy of diazepam was 86%, compared to 100% for the other four drugs
  - Mortality rate significantly lower for the patients given **midazolam** (0%) than other drugs
  - Conclusion **midazolam** might serve as a drug of first choice for the treatment of refractory **status epilepticus**
  - **Higher Reoccurrence rate (50%)**

- Hayashi et al Ped Neuro 2007
- Abend NS -Treatment of Refractory Status Epilepticus: Literature Review and a Proposed Protocol *Pediatr Neurol* - 01-JUN-2008; 38(6): 377-90

Refractory Status Epilepticus

- Valproate Sodium
  - Initial bolus 20-40 mg/kg followed by 2-3mg/kg/hr infusion
  - Hepatotoxicity
  - Hyperammonemia
  - Metabolic Disorders
  - 78%-100% success rate within hour

    - Riviello et al Neurology 2006

Refractory Status Epilepticus

- Propofol
  - 1-2mg/kg/hr loading followed by 1-2mg/kg/hr continuous infusion titrating up to 5mg/kg/hr
  - Hypotension
  - Respiratory Depression
  - Propofol Infusion Syndrome
  - More effective then Thiopental (66% vs 55%)

    - Rossetti et al Epilepsia 2004
    - Parviainen et al ICM 2006

Refractory Status Epilepticus

- Levetiracetam (Keppra)
  - Initial bolus 20-40 mg/kg followed by 2-5mg/kg/min infusion
  - No Drug Interactions known
  - Not metabolized by Liver
  - Well studied in adults

- Szaflarski et al NeuroCrit Care 2007

Inhaled Anesthetics

- Isoflurane and Desflurane
- Dose dependent
- Burst suppression
- Increase recurrence 73%
- Hypotension

Mirsattari et al Arch Neurology 2004

Ketamine

- NMDA blocker
- Takes upto 1-48 hour to effect
- Oral 15 mg /kg /day
- Effect in 48 hours
- Adjunctive Therapy

- Shibuta et al Br J Anesth 2006

Topiramate (Topamax)

- Na and Ca channel blocker
- Independent mechanism
- Takes upto 1-48 hour to effect
- Oral 300-1600 mg /day
- Effect in 48-72 hours
- Adjunctive Therapy

Towne et al Neurology 2003

Special Considerations

- Neonate
  - Rapid Hypoglycemia of the brain despite normal BS
  - Hyperglycemia reduces mortality and developmental impairment effects of SE in newborn
  - Consider pyridoxine

- Abend NS -Treatment of Refractory Status Epilepticus: Literature Review and a Proposed Protocol *Pediatr Neurol* - 01-JUN-2008; 38(6): 377-90

Special Considerations

- **Toxin Relate Seizure**
  - Majority respond to benzodiazepine therapy
  - Pyridoxine should be considered in the treatment of status epilepticus of undetermined etiology
  - Serum glucose determination is critical

- Abend NS -Treatment of Refractory Status Epilepticus: Literature Review and a Proposed Protocol *Pediatr Neurol* - 01-JUN-2008; 38(6): 377-90

Special Considerations

- Pregnancy
  - Lorazepam and Fosphenytoin
  - Birth Defects especially in 1st Trimester
  - Keppra
  - Less risk

- Abend NS -Treatment of Refractory Status Epilepticus: Literature Review and a Proposed Protocol *Pediatr Neurol* - 01-JUN-2008; 38(6): 377-90

EEG Monitoring Beneficial in Emergency Department ?????

Nonconvulsive SE

- Cause of Acute COMA
- 20 % persisting ictal discharges on EEG after cessation of convulsive activity
- EEG for diagnosis
- High Mortality (TBI, Stroke, SAH)
- Important Modifier of Neurologic outcome

- Millikan D -*Emergency Treatment of Status Epilepticus: Current Thinking* Emerg Med Clin North Am - 01-FEB-2009; 27(1): 101-13, ix

Confused ??


I AM LIVING
FAST & FURIOUS 7
IN 2015

Current update

Gretchen et al. Guidelines for the Evaluation and Management of Status Epilepticus. NeuroCritical Care April 2013

Emergent Initial Therapy

IV Lorazepam or IM Midazolam or Rectal Diazepam

IM Midazolam is as effective as IV Lorazepam

Urgent Control Therapy

IV fosphenytoin, Valproate Sodium, Keppra

Refractory Therapy

IV Midazolam, Na Valproate, Propofol, Keppra

Current update

Lacosamide IV

Albers et al Seizure 2011

Our Case

10 yr old with history of epilepsy presents with 10 minute history of generalized tonic clonic activity. Pt received Midazolam by Paramedics and on arrival to hospital continues to seize ?

Midazolam given

Phenytoin or Fosphenytoin

Midazolam Drip

Summary / Key Points

- Seizures >5 minutes --> poor clinical outcomes
- Accelerated Drug Delivery. Lorazepam and phenytoin administrated simultaneously on arrival and progressing directly to general anesthesia if the first-line agents fails to control seizures.
- EEG monitoring in ED for rapid identification of patients in NCSE thereby providing an opportunity for early interventions
- RSE 40% Mortality

The First Hour Belongs to us

ACT FAST

Management

To control seizure activity URGENTLY

Gretchen et al. Guidelines for the Evaluation and Management of Status Epilepticus NeuroCritical Care April 2013


Have A Nice Day

Prehospital Treatment of Status Epilepticus (PHSTE) trial

- Randomized clinical trial (RCT)
- Patients with out-of-hospital seizures lasting longer than 5 minutes
- Randomized to receive intravenous diazepam, lorazepam, or placebo
- Patients given diazepam or lorazepam had early termination of their seizures before arrival in the ED, as compared with patients given placebo.
- Benzo group lower ICU admission (32%) compared to placebo (73%; *P*<.001)
- Higher efficacy and decreased seizure time with intravenous lorazepam as compared with intravenous diazepam

  - Alldredge B.K.et al: Comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital **status epilepticus**. *N Engl J Med* 345. 631-637.2001

Febrile Seizure Clinical Practice Guideline—Febrile Seizures: Guideline for the Neurodiagnostic Evaluation of the Child With a Simple Febrile Seizure (2011 AAP)

- Clinicians evaluating infants or young
- children after a simple febrile seizure
- should direct their attention toward
- identifying the cause of the child's fever.
- Meningitis should be considered
- in the differential diagnosis for any febrile
- child, and lumbar puncture
- should be performed if the child is illappearing
- or if there are clinical signs
- or symptoms of concern. A lumbar
- puncture is an option in a child 6 to 12
- months of age who is deficient in Hib
- and *S pneumoniae* immunizations or
- for whom immunization status is unknown.
- A lumbar puncture is an option
- in children who have been pretreated
- with antibiotics. In general, a simple
- febrile seizure does not usually require
- further evaluation, specifically
- EEGs, blood studies, or neuroimaging

Generalized Convulsive Status Epilepticus in Adults and Children: Treatment Guidelines and Protocols

Emergency Medicine Clinics of North America - Volume 29, Issue 1 (February 2011)

- The formal definition of SE using a 30-minute time frame is not an operational definition; seizure treatment should not be delayed more that 5 to 10 minutes.
  - Early **seizure management** includes checking blood sugar, ensuring oxygenation, and suspecting infection or drug intoxication.
  - First-line therapy for SE includes lorazepam IV (0.1 mg/kg) or diazepam (0.2 mg/kg); if diazepam is used, it should be immediately followed by a loading dose of phenytoin or fosphenytoin.
  - Refractory SE is diagnosed after failure of first-line therapy and treatment should be protocol driven: Choice of medication is dependent on availability, ED capability, and hemodynamic status of the patient.
  - Recommended treatments for refractory SE include: midazolam infusion (0.2 mg/kg bolus then 0.05–2.0 mg/kg/h); pentobarbital (3–15 mg/kg slow push [with hemodynamic monitoring] followed by infusion 0.5–10.0 mg/kg/h; or propofol 3–5 mg/kg bolus, infusion at 1–15 mg/kg/h).
  - An EEG should be considered in patients who have been in convulsive SE to ensure that all seizure activity has ceased.

Shearer P - *Emerg Med Clin North Am* - 01-FEB-2011; 29(1): 51-64

Afebrile Pediatric Seizures

Sherriff GQ - *Emerg Med Clin North Am* - 01-FEB-2011; 29(1): 95-108

- Summary
- Afebrile seizures in children are common and often recur. Fortunately, most children with childhood epilepsy have a favorable long-term prognosis. In particular, patients with idiopathic etiology usually reach remission.[39] There are specific types of afebrile seizure disorders that emergency physicians should be aware of, with absence seizures being the most common. Newborn seizures are often difficult to diagnose, and are evaluated and treated more aggressively than afebrile seizures in older infants and children. Children that present to the ED often have a known seizure disorder, are taking medications for their disorder, and usually are in a postictal state on arrival. Seizures lasting longer than 5 minutes should be treated initially with a benzodiazepine and standard advanced life support protocols. Laboratory studies are needed only in children younger than 6 months, in patients with prolonged seizures or altered level of consciousness, or in patients with history of a metabolic disorder or dehydration. Routine neuroimaging is not recommended in children with a first unprovoked afebrile seizure, although imaging studies should be considered in children younger than 3 years with a predisposing condition or focal seizures. Most well-appearing children can be managed as outpatients after a first afebrile seizure, with instructions for an outpatient EEG and follow-up by the primary care physician. **Anticonvulsant** drugs do not decrease the long-term incidence of epilepsy and are therefore not usually recommended after a first afebrile seizure. New **anticonvulsant** drugs continue to be investigated, but it is important to recognize that no anticonvulsive agents decrease the long-term incidence of epilepsy and are therefore not usually recommended after a first afebrile seizure. Adjunct nonpharmacologic therapies such as vagal nerve stimulation are also being used in patients with severe epilepsy. Intermittent electrical stimulation is delivered to the cervical vagus nerve. The lead is usually located on the left side of the neck, and the generator is implanted in the chest wall. The emergency provider should keep abreast of new technologies and emerging trends in pharmacologic antiepileptic management.

Afebrile Pediatric Seizures

Sherriff GQ - *Emerg Med Clin North Am* - 01-FEB-2011; 29(1): 95-108

- **Key concepts**

- ● An EEG should be performed as soon as possible on patients with an apparent first unprovoked seizure.
  ● Electrolyte testing is not routinely necessary on well-appearing children older than 6 months.
  ● Emergent neuroimaging of children with first-time seizures should be performed on patients with the following risk factors: focal seizures, prolonged postictal period, status epilepticus, sickle cell disease, immunocompromise, head injury, age less than 6 months to 1 year, ventriculoperitoneal shunts, recent travel to an area endemic for cysticercosis, bleeding disorders, cerebral vascular disease, neurocutaneous disorders, malignancy, HIV, or hydrocephalus.
  ● Well-appearing children who have experienced a first unprovoked seizure and are in the low-risk category do not need emergent neuroimaging if they have close outpatient follow-up.
  ● Children on ketogenic diets should not be given dextrose empirically.

Specific Considerations

Buccal Midazolam vs Rectal Diazepam

- Randomized controlled Trial
- Children aged 6 months and older with active seizures and without intravenous access
- 219 episodes
- Therapeutic success was 56% (61 of 109) for buccal midazolam and 27% (30 of 110) for rectal diazepam
- Rate of respiratory depression did not differ
- Buccal midazolam was more effective than rectal diazepam

McIntyre J., et al: Safety and efficacy of buccal **midazolam** versus rectal diazepam for emergency treatment of seizures in children: *Lancet* 366. 205-210.2005

Intranasal Midazolam compared to IV benzodiazepines?

- Lahat et al.
  - randomized controlled
  - diazepam, 0.3mg/kg IV, or midazolam 0.2 mg/kg intranasally
  - Midazolam 88% 6.1 mins
  - Diazepam 92% 8.0 mins
  - Safe, effective no difference in adverse events
- Mahmoudian T. et al ,
  - Midazolam (0.2 mg/kg) to IV diazepam (0.2 mg/kg)
  - 70 patients (ages 2 to 15 years)
  - Both methods were equally effective, and no adverse effects occurred in either group.

Lahat E., *BMJ* (2000) **321** : pp 83-86.
Mahmoudian T. et al , *Epilepsy Behav* (2004) **5** : pp 253-255

lorezapam

- Lorazepam can be given across mucus membranes (rectal, nasal, or buccal)
- NIH Randomized controlled trial
  - lorazepam not effective when given by transmucosal routes to patients who have SE The National Institutes of Health, 2008.

Mucosal lorezapam not EFFECTIVE

Phenytoin

- Phenytoin
  - Lipid soluable
  - Peak brain levels in 6 mins
  - Variation in metabolism in subjects
  - S/E
    - Arrhythmia
    - Hypotension
- Fosphenytoin
  - Water soluble
  - I/M route
  - Rapid administration

Phenobarbital

- Cerebral uptake is enhanced by seizure activity
- Long half life, 50-150 hrs
- Difficult to assess neuro activity
- Hemodynamic instability

Current update

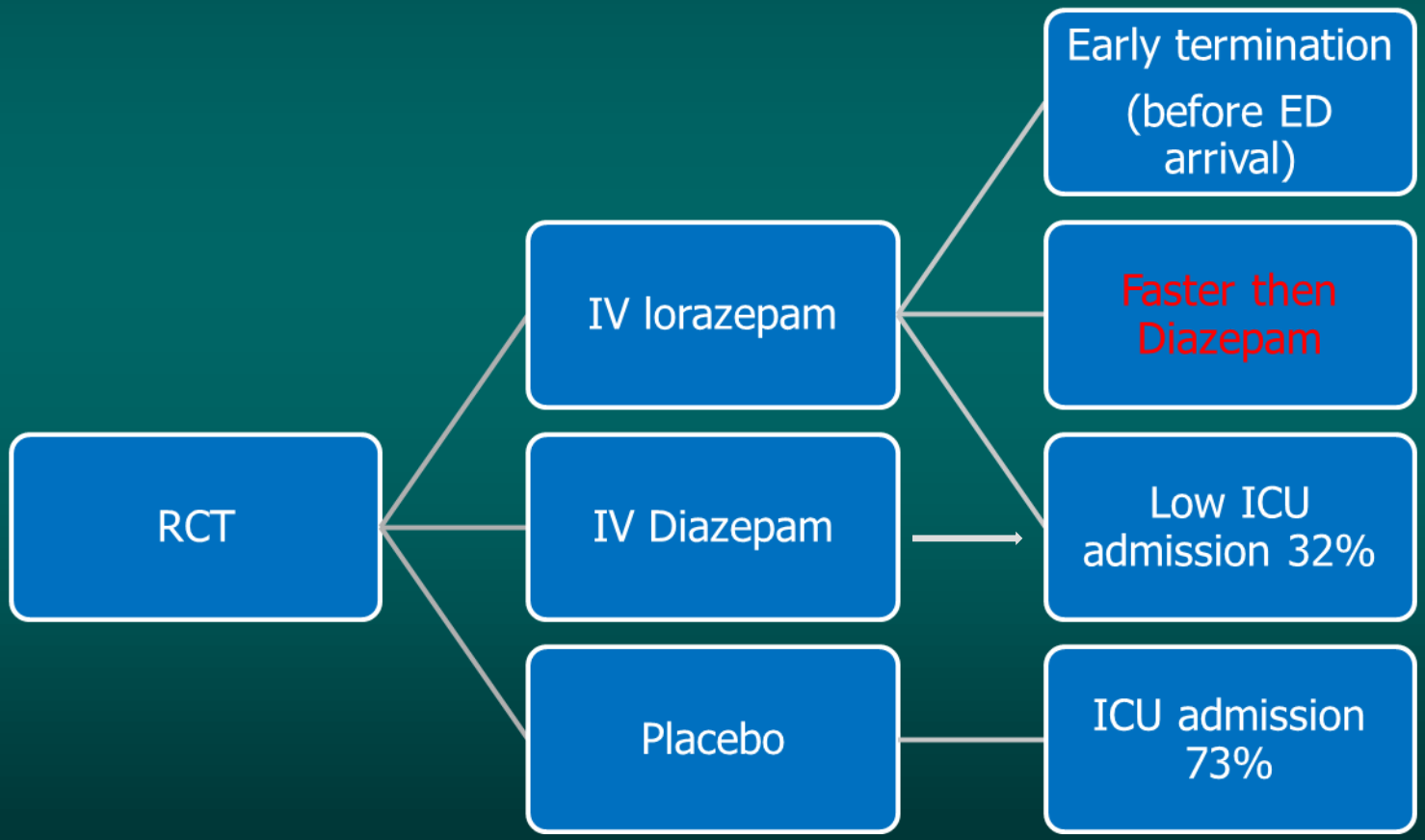
Chamberlain et al. Lorazepam vs Diazepam for Pediatric Status Epilepticus JAMA 2014

No difference

Critiques

1. Second dose of Diazepam (Half what is usually given)
2. Respiratory Depression more in Diazepam group
3. More sedation in the Lorezapam group

Prehospital Treatment of Status Epilepticus (PHSTE) trial



Alldredge B.K.et al: Comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital **status epilepticus**. *N Engl J Med* 345. 631-637.2001

Prehospital Treatment

- Midazolam or Lorazepam in Prehospital setting ??
  - No storage problems
  - Effective when given intramuscularly or other transmucosal routes
  - Dosing is likely to be 0.2 mg/kg for children in preliminary trials
  - Cheaper then lorazepam

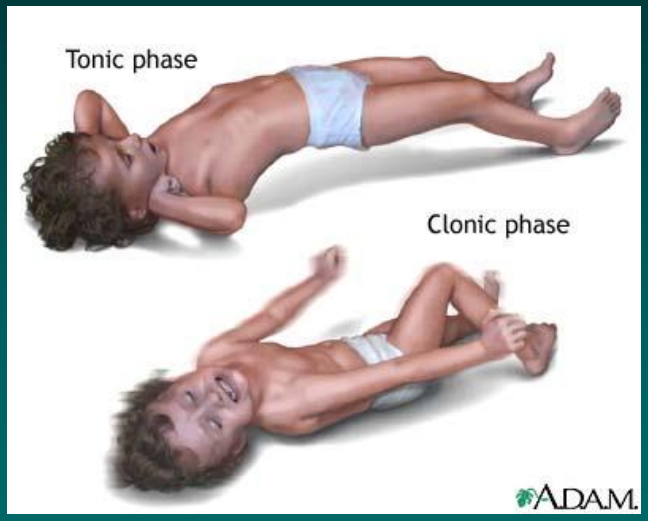
- Rainbow J., Browne G.J., Lam L.T.: Controlling seizures in the prehospital setting: diazepam or midazolam?. *J Paediatr Child Health* 38. 582-586.2002;

Clinical presentation

- Acute
  - Poor response
  - Higher mortality
  - Sepsis, metabolic, CNS infections, stroke, head trauma, drug toxicity, hypoxia
- Chronic
  - Better response
  - Lower mortality

Shearer P - *Emerg Med Clin North Am* - 01-FEB-2011; 29(1): 51-64

Type of Seizure

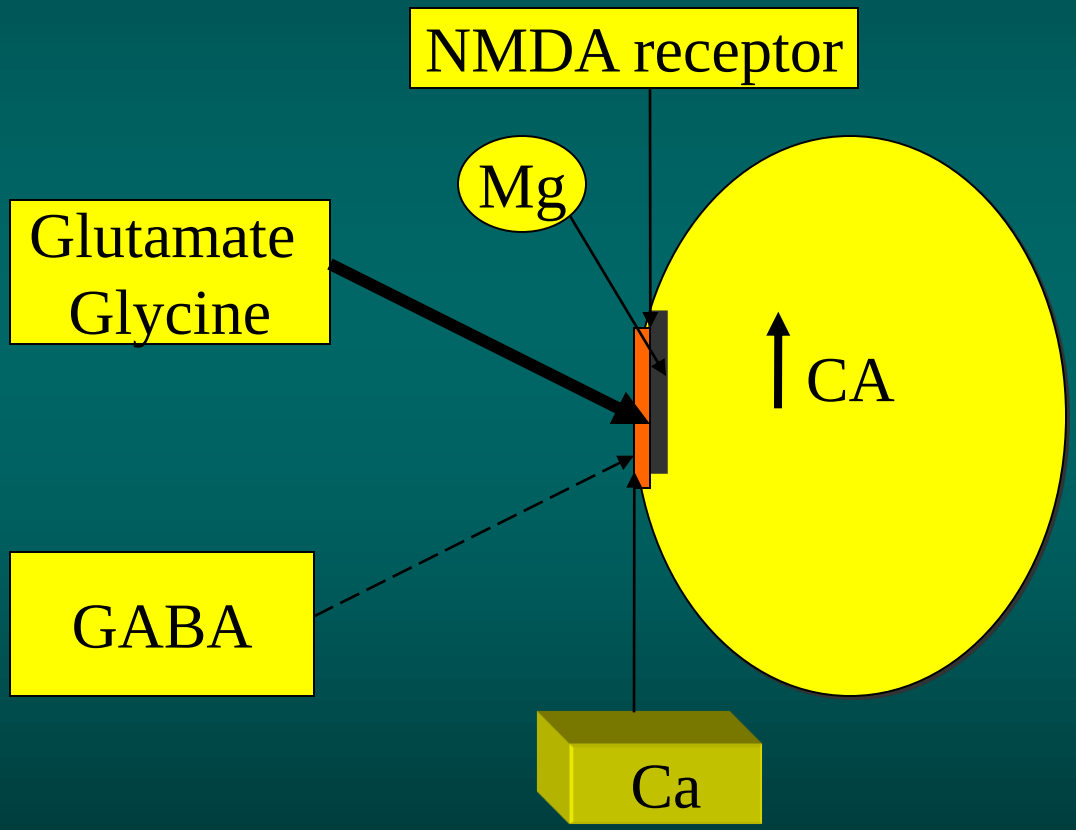


- Convulsive
  - Generalized
    - 90% with loss of consciousness
  - Partial

- Nonconvulsive
  - Absence or complex Partial Seizures
  - 10% episodes
  - 14% post convulsive SE

- Goldstein J - Status Epilepticus in the Pediatric Emergency Department *CPEM* - June 9(2); 96-100, 2008;

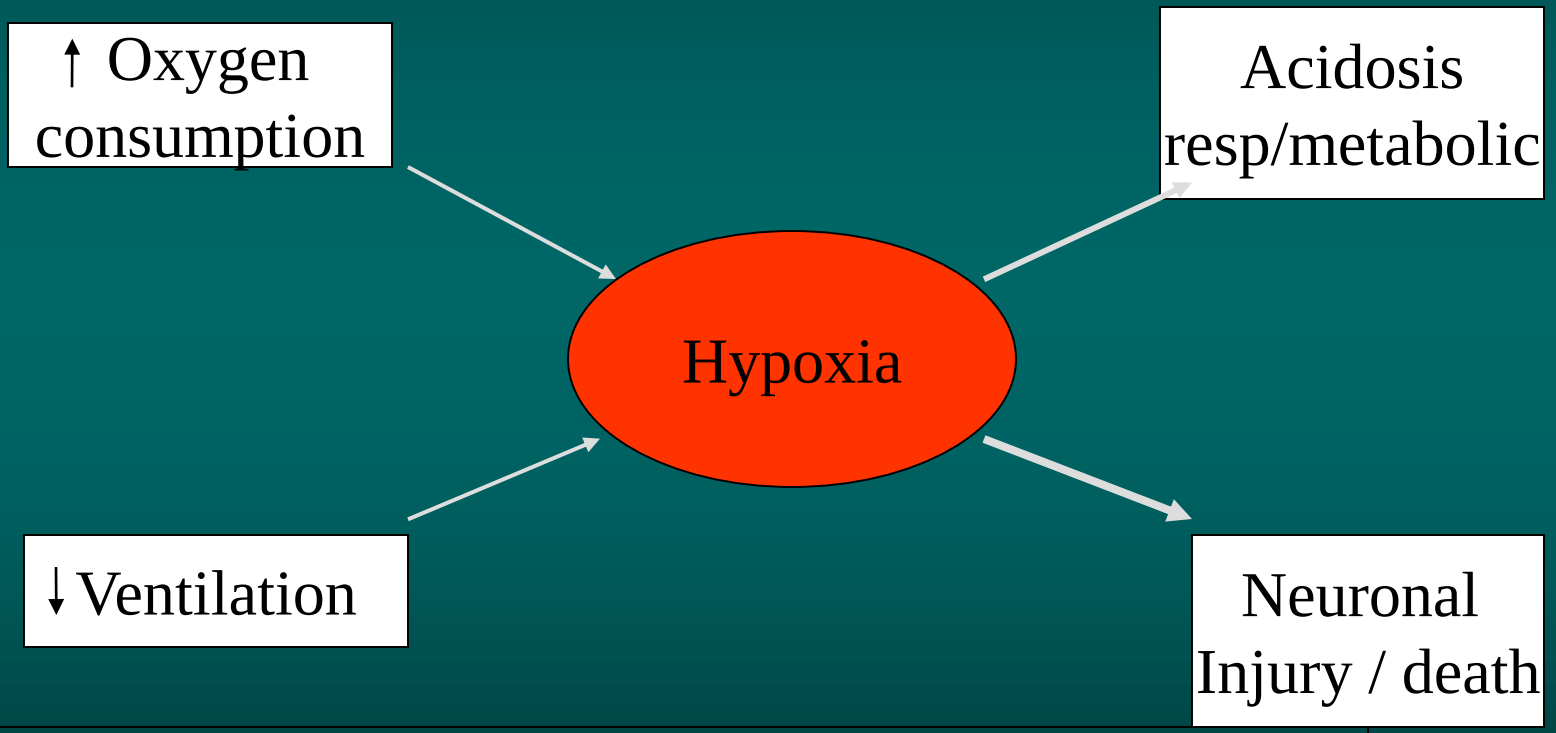
Excitatory Inhibitory Receptor interaction



SE >30 mins
Ca induced cytotoxcity
Neuronal Damage

▪Goldstein J - Status Epilepticus in the Pediatric Emergency Department *CPEM* – June 9(2); 96-100, 2008;

Refractory Status Epilepticus



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