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Clinical Question: Second Line Agent in Status Epilepticus: Phenytoin or Valproate

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Abstract

In this article, we have tried to review the evidence regarding the use of second line agents in status epilepticus, comparing phenytoin and valproate in particular. While phenytoin continues to be used as the preferred second line agent, valproate is equally effective and safe. However, there is need for generating more evidence particularly with respect to safety profile of these two drugs in comparison to each other so that, a consensus may be arrived at in future as to, which is the best second line drug among these two agents in terms of both safety and efficacy.

Keywords: Phenytoin, Valproate; Status epilepticus; Second line agents; Diazepam; Midazolam.

Case scenario

A 5 year old child was admitted to pediatric emergency unit with generalized seizures from last 15 minutes. There was no history of fever, vomiting, headache or head injury. On examination child was unconscious and generalized tonic–clonic movement were seen along with frothing from mouth.

Child was stabilized and was put under oxygen. Immediately after accessing IV line benzodiazepam loading dose was given. Seizures continued for 5 minutes. Now what should be the management strategies?

1) What should be our second line drug; Phenytoin, Valproate or others?
2) What is the evidence of second line drug for SE?
3) How should we monitor the patients?
4) Any future or newer therapeutic modalities are available?

Let us briefly review the evidence to answer the above questions…..

Introduction

Status epilepticus is a major neurological emergency with an incidence of about 20/100,000 and mortality between 3 and 40 % depending on etiology, age, status type, and status duration.[7] Benzodiazepam and Phenytoin/Fosphenytoin are traditionally used as first line drugs and are effective in about 60% of all episodes. However, a notable portion of patients remain in SE. unfortunately, high level evidence is available only for the first-line medication; in particular for lorazepam which had been shown to be more effective than phenytoin (PHT) or placebo.[2,9] However, because first line therapy fails to control at least 35-45% of patients with SE[2], additional treatment are needed, for whom convincing evidence is lacking. Historically, phenytoin[1] has been used before valproic acid (VPA)[3,4] as a second-line agent.

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Table 1: Common etiology of status epilepticus in children

1. Acute
• Acute CNS infection (bacterial meningitis, viral meningitis, encephalitis)
• Metabolic derangement (hypoglycemia, hyperglycemia, hyponatremia, hypocalcaemia, anoxic injury)
• AED noncompliance or withdrawal
• Prolonged febrile convulsion (23%–30%)
2. Remote
• Inflamatory granuloma
• Cerebral migrational disorders (lissencephaly, schizencephaly)
• Perinatal hypoxic-ischemic encephalopathy
• Progressive neurodegenerative disorders
3. Idiopathic/cryptogenic

A small prospective randomized study[5,6] analyzed PHT and VPA after diazepam failure and showed that both drugs were surprisingly highly effective (controlling SE in 88% and 84% of patients, respectively). More recently, levtiracetam (LEV)[7,8] has also been described for this indication, but again without any comparison to other agents. To address this relevant lack of information, we searched medical database to investigate the relative role of PHT, VPA and LEV in the treatment of SE as second line agent.

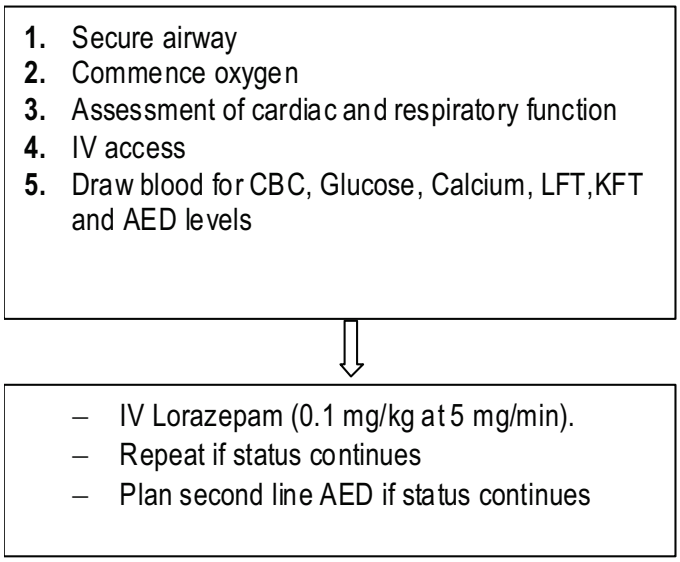
Definition

SE is defined as a single seizure lasting more than 30 minutes or repeated seizures over a period of more than 30 minutes without gaining consciousness. However, for practical reasons, this definition was recently modified by working group on status epilepticus[4]: particularly for generalized seizures, seizures activity persisting for more than 5 minutes is considered to be SE and should be treated accordingly.[9]

Epidemiology

The average incidence of SE is at least 20/100,000 for the Caucasian population in industrialized countries.[7] The incidence from developing world is lacking. The incidence of SE has a bimodal distribution, with the highest incidences during the first year of life and after the age of 60. Among children, babies younger than 12 months had the highest incidence and frequency of status epilepticus. The most common cause in children is febrile seizures or infections, accounting for more than 52% of pediatric cases (Table 1). Remote symptomatic cause and low antiepileptic drug levels account for another significant percentage in children. Patient age at diagnosis, etiology of SE, severity of underlying disease, and duration of SE are the main predictors of increased short term mortality.[11-13] Therefore early and aggressive treatment is very important for successful management.

Flow chart showing initial management in status epilepticus



Management of SE

Initially airway, breathing and circulation should be stabilized, blood sugar should be checked and oxygen should be administered. Then, an intravenous line should be placed for the injection of medication and to draw blood samples (glucose level, electrolyte, blood count, liver and kidney function test, drug levels and toxic drug screen). A screening neurological should be performed for signs of focal or diffuse intracranial lesion. Before aggressive treatment is initiated, possible differential diagnosis should be considered. Treatment can be divided into two parts: initial treatment in the emergency room, second line drug for treatment failure.

Initial treatment in the emergency room

Benzodiazepines

The benzodiazepines most commonly used for the treatment of SE are diazepam (DZP), lorazepam (LZP), and midazolam. LZP is less lipophilic; it has a smaller volume of distribution and a longer intracerebral half-life (12 hours) as compared with DZP (15-30 minutes) and therefore, a potentially longer anticonvulsive effect. Several studies have compared the effectiveness of lorazepam and diazepam in the treatment of status epilepticus.[9,14] Most studies have found non-significant but relevant difference in favor of LZP. In children, treatment with intravenous LZP in the emergency department was associated with a 3.7 times (95% CI: 1.7-7.9) greater likelihood of seizure termination than was treatment with rectal diazepam (10). In accordance with these data and a recent Cochrane review[15] we consider LZP the first line benzodiazepine in SE. If SE persists after 20 minutes, benzodiazepine treatment should be followed by second line anticonvulsant.

Second line drug for treatment failure

Traditionally, benzodiazepine treatment is followed by 15-20mg/kg of intravenous phenytoin given at a maximal infusion speed of 50 mg phenytoin/minute.[16] No randomized controlled data supporting phenytoin as a second line treatment are available, but one uncontrolled study suggested that 50% of patients not successfully treated with benzodiazepine alone would respond to second line treatment.[17] Traditionally, based on a long clinical experience, and case controlled study, intravenous phenytoin has been used as the second line drug.

Starting in the 1980s, the use of intravenous valproate has been reported in an increasing number of uncontrolled case series, indicating relatively ease of use; good tolerability and suggesting that it may be efficacious.[18 In one

Table 2: Summary of the studies showing comparison of valproate and phenytoin in status epilepticus

Source/authors	classification	Level of evidence	Results	conclusion
Agarwal *et al*. seizure. 2007 sep; 16(6): 527-32	RCT	Ia.	100 patients with diazepam refractory SE received either IV phenytoin or IV valproate loading dose of 20mg/kg at 40 mg /min. 88% had control of SE vs. *84% for phenytoin. No hypotension or respiratory depression was seen in valproate group, although mild elevation in liver enzymes was found in 4/50 pts.	IV valproic acid is as effective and has better tolerability than IV phenytoin when treating benzodiazepine resistant status epilepticus.
Yu *et al*.Epilepsia. 2003 may; 44(5): 724-6	Retrospective review	III	18 pediatric patients with lorazepam resistant SE received 25mg /kg/min of valproic acid. All had seizure cessation within 20 minutes.	Valproic acid bolus of 25mg/kg at 3 mg/kg/min is safe and effective for the treatment of SE in children.
Mehta *et al*.j child neurol.2007 oct;22(10):1191-7	RCT	Ia.	Open-label RCT of 40 children with refractory SE (diazepam+phenytoin)received valproate 30mg/kg over 2-5 minutes or diazepam infusion. Time to control seizures was 5 minutes in valprote group vs. 17 min. in diazepam group.	IV sodium valproate is an effective alternative to diazepam in controlling refractory status epilepticus in children and is without any complication.
Alvarej V *et al*. Epilepsia 2011: 1-5	Retrospective review	III	Study analyzed 187 episodes of SE in which PHT, VPA or LEV were given. VPA failed to control SE in 25.4%, PHT in 41.4% and LEV in 48.3% episodes. LEV failed more often than VPA(OR 2.69; 95%CI 1.19-6.08).	Leveracetam seems less effective than valproate to control SE after benzodizepines.
Rai A *et al*. pediatric neurology 2011;45 :300-304	RCT	Ia.	100 children with motor focal seizures or generalized seizures were randomized to receive valproate or phenytoin. The primary end point efficacy was 93% and 97% respectively. Time to regain consciousness was less in valproate group.	IV valproate is safe and efficacious with less time to regain consciousness.
Gilad± R *et al*. acta neurol scand 2008; 118: 296-300	Case series	III	Seventy-four adult patients with SE participated in the study, 49 with VPA and 25 PHT . In 43 (87.8%) of the VPA patients, the seizures discontinued. Similar results were found in the PHT group in which seizures of 22 (88%) patients were well controlled. Side effects were found in 12% of the PHT group, and in none of the VPA group.	VPA i.v. seems to be effective and well tolerated in adult patients with SE or ARS.
Misra *et al*. neurology 2006; 67: 340-342	Pilot study	III	Sixty-eight patients with SE were randomly assigned to two groups to study efficacy of sodium valproate and phenytoin. Seizures were aborted in 66% of valproate group and 42% in phenytoin group.	Sodium valproate may be preferred in SE because of its higher efficacy.

study, 20 adult patients in acute or static SE with generalized tonic-clonic seizures or simple partial motor seizures were administered IV valproic acid in a bolus dose of 1mg/kg/h for 24 hour safely. SE was interrupted in less than 30 minutes in 80% of cases.[19 Recently, there are other reports about successful use of IV valproate in controlling SE. we searched Cochrane database of systematic reviews but could not find any reviews comparing the two in SE.

No other systematic reviews or meta-analysis were found in children comparing phenytoin versus valproate as a second line drug for management of SE. However a number of controlled and descriptive studies have been reported on the efficacy/safety of these drugs, the findings of which are summarized below (Table 2). There are no trials on use of lacosamide in SE. An initial intravenous replacement trial in 60 patient showed the LCM was well tolerated when given over 30 or 60 minutes.

Conclusion

Having reviewed the available evidence following recommendation can be made

1. Valproate is as effective as Phenytoin in controlling status epilepticus(SE) in children (class I).
2. Valproate may be safer than Phenytoin but class I evidence are lacking. In all the RCT the difference in safety profile was not significant because of small sample size.
3. Valproate should be avoided in hepatic failure and metabolic disorder. Patient should be monitored for cardio respiratory parameter especially when phenytoin infusion is given.
4. Leveracetam is less effective than sodium Valproate in controlling SE.(class III evidence; adults).

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