Status Epilepticus

Special Guest: Karen Berger, PharmD, FCCM, BCPS, BCCCP

How did you become interested in the management of Status Epilepticus (SE)?

- Pharmacists can have a dramatic impact
- Able to use highest level of Pharmacist knowledge (drug selection, MOA, non-standard dosing, monitoring, drug interactions, titrations, etc)

How does SE differ from a seizure?

- Seizure – abnormal electrical disturbance in the brain
- SE – prolonged seizure activity
  - Previously defined as 30 minutes of continuous seizures
  - Recently revised to 5 minutes or more of continuous seizure activity
    - Seizure activity can be clinical or electrographic (only visible on EEG) or recurrent seizures where the patient does not return to their baseline between seizures
- When referring to SE (e.g. review articles), typically it’s referring to generalized SE where the whole brain is involved
  - Not focal SE that only involves one focal part of the brain and may be less neurotoxic
  - The management between these types of presentation differs

Are there different classifications of SE?

- Refractory SE – seizures persist despite 2 anti-epileptic drugs (AED) generally defined as a BZD and one-additional AED
- Super-refractory SE – not as clearly defined in the guidelines
  - When SE persists despite infusion of IV anesthetic

How do patients in SE typically present?

- Two typical presentations
  - Convulsive SE – tonic-clonic movement and rhythmic shaking
    - Similar to what you would see in movies/TV shows
Non-convulsive aka Sub-clinical SE – no clinical/visual evidence of SE but there is EEG evidence of SE

**Can the presentation change throughout the course of the hospitalization?**

- Yes, the presentation can vary throughout the hospitalization
- This is why it’s critically important these patients receive continuous EEG monitoring
  - Can present with convulsive SE, and the convulsions stop
  - However once placed on continuous EEG you may see that they are still in SE, just not with convulsive seizures

**Are there disease states or risk factors for status epilepticus?**

- Yes, and this is why it’s so important to get a good history from the patient and/or their family
- Patients with epilepsy who are non-compliant with AED is the most common cause
  - Can also affect patients with epilepsy who are compliant (breakthrough seizure may progress to SE)
- Other risk factors include:
  - Neurologic injury (TBI, ICH, SAH, meningitis)
  - Electrolyte disturbances (Na, Glucose)
  - Hypoxia (Post-cardiac arrest)
  - Auto-immune encephalopathy
  - Drugs of abuse
  - Medications

**What are common medication-induced causes of SE?**

- Important to verify all medications (especially if it’s easy to discontinue)
- Common offenders include:
  - Penicillins
  - Cephalosporins
  - Carbapenems
  - Anti-psychotics (e.g. Clozapine)
  - Anti-depressants (e.g. TCAs, Lithium)
  - Flumazenil
Which disease states/risk factors necessitate urgent non-AED treatment for SE?

- Electrolyte abnormalities
  - Sodium or glucose disorders which could be easy to treat immediately
- Alcohol withdrawal
- Receiving medications that could be causing/contributing to SE
- If no clear cause, may start empiric treatment for meningitis
- A lot of AED may be treating the true seizure pathology, but identifying and treating the underlying cause will be the true SE treatment
- This is why determining the etiology of SE is so important

Do you empirically treat for Wernicke’s encephalopathy in patients with an unknown history?

- We can, but it would be considered an adjunct treatment to the SE algorithm
- Less of an effect on the initial treatment
- May influence how many AED they are prescribed when ultimately discharged from the hospital
  - Patients who present with alcohol withdrawal seizures will generally be discharged with at least 1 AED

What is your preferred BZD for initial treatment of SE?

- Guideline-recommended BZD lorazepam is her preferred agent
  - Guideline-recommended lorazepam dosing: 0.1 mg/kg up to 4mg
  - Many still underdose lorazepam: ~15% of patients in a recent study received the full recommended dose
- The patient’s IV access does affect this answer ultimately
  - If no IV access: preferred BZD is IM midazolam
  - IM Midazolam which was shown to be superior to IV lorazepam

If patients in SE don’t respond to the initial BZD (assuming it was dosed correctly), do you avoid future administrations of this specific agent?

- No, definitely not
- BZD and repeat doses of BZD are first-line treatment for SE
- If patients are refractory to the above (BZD + repeat BZD doses), then it is followed closely by adding an AED
o If patients are still refractory to those interventions, consider intubation and escalate care

- There could be many reasons why the patient didn’t initially respond:
  o Could be an ineffective initial dose
  o Patient may already be in refractory SE, but the medication may be having some effect
- If an AED was ineffective, would add additional AED with differing mechanism of actions if possible
  o Hesitate to discontinue any AED that have been implemented for SE
  o Don’t know if they were truly ineffective or if they had a partial effect
    ▪ Patient may have had 50 seizures, but without the AED they would have had 100

How can we help convince providers to use larger more evidence-based BZD doses?

- Having an institutional policy/guideline and an electronic order set can greatly help
  o Prevents delays in order verification
  o Help others feel more comfortable with the higher doses
- Many drug information resources such as Lexi-Comp recommend doses that are widely different from guideline-recommended or evidence-based AED dosing in SE
- For BZD in particular, education is critical
  o Even in an RCT, we aren’t effectively dosing BZD
  o Underdosing BZD can actually be worse compared to the theoretical risks of overdosing (e.g. respiratory depression or oversedation)
    ▪ Patients who receive BZD actually have less cardiac/pulmonary side effects compared to placebo
  o Almost prefer to intubate due to overdosing BZD (although this is very rare) rather than underdose a patient in SE
    ▪ Because the longer you are in SE, the harder it is to treat
Does your initial/repeat BZD dosing change in patients who chronically use alcohol or BZD?

- Generally it doesn’t
- May make the team more comfortable in giving the full guideline-recommended dose
- Or the team may re-dose/re-challenge these patients with a repeat BZD dose quicker than normal

What is your first-line AED for patients in SE?

- Her institutional guidelines recommend Valproic Acid (VPA) or Phenytoin (PHT) a little higher than Levetiracetam (LEV)
  - But ultimately it will be a team decision
  - Data to guide AED selection is very minimal
- Can use patient-specific factors to help guide therapy
  - Organ dysfunction and drug-drug interactions
- Ultimately, the huge remaining unknown question is which of those three AEDs (PHT, VPA, LEV) should be first-line
- Generally speaking, the best agent is the one you can get the fastest
  - Many clinicians do prefer PHT or VPA
  - But if you can get LEV from the Omnicell/Pyxis immediately, that is the drug of choice
  - Drug-interactions will also factor in, two of the most common include:
    - VPA – Meropenem
      - One dose of meropenem can cause VPA levels to be undetectable
    - PHT – Nimodipine
- ESETT trial will help guide which AED should be given first-line

Why is it so difficult to have high quality research on AED in SE?

- It is challenging for multiple reasons:
  - The mixed etiologies and varying severity of illness
  - Identifying and recognizing SE is difficult
    - There are also patients who may have been in sub-clinical SE with no idea of how long they have been in SE which will confound the data
  - Variety of treatments you can use
- Some RCTs have been attempted but terminated due to lack of enrollment
Because there are so many factors that may play a part, it’s hard to say that one intervention definitively caused a positive result or treatment benefit.

Are there any patient populations or disease states where you prefer or avoid a specific AED?

- Generally it is all related to drug interactions when initially picking an AED.
- The SE algorithm is developed to start first-line treatment as fast as possible:
  - Over time, as you start to add additional AEDs and move down the algorithm, you may be more thoughtful.
- In the initial stages, it is most important to get the drug to the patient as fast as possible.
- If you vary from the algorithm, the medication may not be in the Omnicell/Pyxis or there may be a delay because the Pharmacy isn’t used to verifying this order:
  - This could all be based on theoretical risks/benefits that we’re not sure will actually pan out.

Why is timely treatment so important in SE?

- SE progresses very quickly and pharmacoresistance can occur through receptor trafficking.
- Agents that we initially provide are GABA agonists (e.g. BZD):
  - Even if they initially work, over time they are less effective or not effective at all.
  - Studies have shown that the response to AED can diminish very quickly.
- Longer you are in SE, the harder it is to break.
- If we miss the golden window in the first 30 minutes to 1 hour, you have to play catch up and be more aggressive later on.

Levetiracetam

- Popularity and use has increased greatly over the past few years.
- Guidelines recommend a 1-3g LD:
  - Commonly use a 2g LD.
- ESETT trial is using a weight-based LD (up to 4.5g):
  - Most institutions don’t go that high.
- Not many things to worry about after administration:
  - Renally eliminated:
    - Dose reduce if patient is in renal failure or on iHD.
Biggest ADE is behavioral disturbances
  - Don’t consider this until much later in their course (e.g. when deciding which AED to try and taper off)
  - No real drug-drug interactions

Phenytoin/Fosphenytoin

- We may use PHT because we have used it so much historically
  - However, due to lack of RCT data in SE, clinical experience is important
  - Have been using PHT for many years and it is effective as seen clinically and in retrospective studies
- Typical PHT loading dose: 20 mg/kg
- Fosphenytoin is the prodrug of Phenytoin
  - Some say Fosphenytoin may be better because you can administer it quicker
    - Remember, Fosphenytoin needs to be converted to phenytoin which will take some time
- There are so many nuances with Phenytoin
  - Rate of administration: Max 50 mg/min
  - Formulated with propylene glycol
  - Only compatible with Normal Saline
  - Must have a specific concentration when compounded to be stable
  - Narrow therapeutic index (TI) medication that requires close monitoring with PHT levels
    - Due to the narrow TI, the team may push PHT levels a little higher
    - But don’t want to be too aggressive due to risks with supratherapeutic levels
- Fosphenytoin has some advantages over Phenytoin
  - Faster administration time: 150 mg/min
  - Better compatibility with other diluents
  - Can give IM or IV
  - Lower doses could be given IVP (not requiring a diluent)
- Fosphenytoin is their loading dose agent of choice
  - Higher doses of phenytoin can cause hypotension and arrhythmias during administration, which can be reduced when using Fosphenytoin instead
- Phenytoin is the maintenance agent of choice
- There is no nationwide consensus on using one or the other or a mix of the two
Valproate Sodium

- Potential for hepatotoxicity or hyperammonemia may lead prescribers to avoid using VPA
- Clinically, many providers choose PHT or VPA (one or the other)
  - Drug interaction between PHT and VPA is significant and also changes over time
  - Keeping these AED levels therapeutic can be challenging even for the best pharmacist
- Most use a higher LD: 40 mg/kg
  - Lower LD 20 mg/kg and possibly need to re-load
- If you have a patient receiving a carbapenems, keeping the VPA levels therapeutic can be challenging with a large risk of the patient going back into SE
  - When a patient is receiving these concomitantly, if you wait until the morning to check a VPA level it is probably too late

Lacosamide

- Not a first-line AED, but many algorithms list this as a second-line agent
- LD: 200-400 mg
  - Small study demonstrating a benefit with 400 mg
    - Earlier termination of seizures
    - But overall no difference in clinical outcomes
- Can administer Lacosamide IV push (IVP)
  - Study showed a reduction in time to administration from 2 hours when given as IVPB to 35 minutes as IVP
- ADE: PR prolongation
  - May over-estimate its incidence
  - Something to consider in patients with baseline or acute cardiac issues
- No drug interactions and no real dose adjustments
- Transition of care consideration: expensive and may not be covered by insurance
  - Shouldn’t affect initial selection but could affect which AED is discontinued when tapering them off

Brivaracetam

- Seems to be a “me too” agent, similar to levetiracetam
- No real scenario when this would be used including:
Instead of LEV
After failing LEV therapy
- Dose adjustments for hepatic impairment
- Multiple DDI including: phenytoin, phenobarbital
  - These clinical issues aren’t seen with levetiracetam
- Not great data in SE, mainly case series

- For all of the AED agents for SE, will not hepatically or renally adjust the LD
- Goal is to administer the loading dose as quick as possible

Where to find evidence-based dosing recommendations for AED medications in SE?

- Guidelines are a great starting point
  - However they may be outdated as higher doses are consistently being studied for these agents
- Best recommendation would be an updated review article
  - Multiple articles that are released every year
  - Can broadly look at evidence-based medicine without looking at each individual reference
- Each institution likely also has a protocol/algorithm that they use which is individualized to that particular center
  - This is the most helpful thing to do
  - Input from all disciplines (Neurology, Neurocritical Care, Pharmacy, etc)
  - Order sets are built and these AED are kept in Pyxis/Omnicell for easy access
    - In a condition like SE where there isn’t evidence that necessarily says one agent is better than the other
    - Administering these agents as fast as possible and avoiding delays is the most important thing
- Using institutional protocol and keeping that protocol up-to-date with the best evidence is the best approach
What are best-practice recommendations for AED TDM and what to do when you are limited with laboratory resources (e.g. not having free levels but total levels)

- When patients come in, should get admission AED levels even if they don’t come back right away
  - If the levels return low, could ultimately guide SE treatment
  - Even could consider obtaining a LEV level
    - Can use to see if patient is compliant, not to guide potential dose adjustments
- Get post-loading dose AED level and total AED level
  - Not dosing these agents for epilepsy, so levels are being drawn at least daily initially rather than every 7 days
- When free levels are a send-out:
  - There is still utility to obtaining these AED free levels
    - Particularly in patients with renal dysfunction or low albumin levels
  - More data being published that equations adjusting total AED levels for albumin are inaccurate
- Order free and total at the same time
  - When the free level returns, create a ratio of total:free and apply that to future total AED levels
  - This can help reduce potential toxicities from supratherapeutic levels with these AEDs

When do you decide to increase the dose or add an additional AED for patients in SE who don’t respond to the initial management (BZD + AED)?

- Generally they do both
- May check a level, give a mini-loading dose, or increase the maintenance dose to optimize the current AED
- Would also add an additional AED
  - Clinically it is difficult to say it was simply a dosing issue
  - Level may take too long to come back
    - So unless you have the opportunity to give a mini bolus based on a level, may empirically add an agent
  - Can titrate these AED down when the patient recovers
- Generally don’t switch agents, even if the patient doesn’t respond
- Keeping in mind that they could have had even more seizures if not for that AED
  - In early stages of SE, poly-pharmacy is not a concern
    - Adding multiple agents in sequential order
    - Next step is intubation and IV anesthetic continuous infusion

### What tips/tricks are there to improve the timely treatment of SE?

- IV push dosing is becoming popular
  - Especially for levetiracetam and lacosamide
  - Also lower doses of fosphenytoin can be given IVP (e.g. mini loading dose)
- If patient is intubated already, never hurts to start a continuous infusion
  - We can forget how long it takes for the AED medication to be ordered, verified, and administered
  - Propofol can be pulled on override and initiated almost immediately
    - The tougher decision is for patients who are not intubated
- Loading commonly used AED in the Omnicell/Pyxis machine
- Using Add-Vantage bags
- Having institution-based guidelines, protocols, and order sets
- Early identification of SE patients and making sure the team is on the same page
  - Order medications stat and limit delays in order verifications due to the higher doses being used in SE
  - Think of this as a neurologic emergency

### When patients are in refractory SE, what is the general algorithm in regards to IV anesthetic infusions?

- The data suggest that these three agents would be acceptable:
  - Midazolam
    - Many consider this first-line due to the ADE from the other agents
    - Can take the patient a long time to wake up after being on much higher doses for longer periods of time
  - Propofol
    - Many side effects such as PRIS and hypotension
      - Especially with the higher infusion rates being used in SE
    - But could use as the initial agent due to its quick availability from the Omnicell/Pyxis and then switch to midazolam
o Pentobarbital
  ▪ Limited in use due to the large amount of side effects
    • Hypotension is commonly seen
o Ketamine can be considered an add-on agent
  ▪ Not used as a first-line IV anesthetic
  ▪ More data supporting its efficacy
  ▪ More favorable side effect profile
    • Much less likely to experience hypotension
    • Hypertension may happen, which could lead to faster vasopressor discontinuation
  ▪ Can also extubate patients who are receiving ketamine

▪ Getting the patients out of SE is the most important thing
▪ One question is whether patients should have burst suppression or simply seizure suppression?
  o Burst suppression can lead to complications such as infection due to the therapeutic coma
  o No goal has been identified as superior to others
▪ If you initiate the continuous infusion and seizures stop, could keep the infusion rate/dose the same
  o If seizures continue, may need to increase the dose from targeting seizure suppression to burst suppression

**What are things that Pharmacists can do to help treat patients in SE?**

▪ Can assist in every part of the process
▪ Work on the SE protocol and order set
▪ Assist in agent selection and dose optimization
▪ Dose adjust for renal/hepatic impairment or drug-drug interactions
▪ Getting involved with research and education
  o So much opportunity to optimize therapy and get therapy to patients faster if they know what to look for and what to do
What are take-home points in regards to the treatment of SE?

- Be Fast
  - Drug of choice is the drug you can get to as quickly as possible
  - Don’t worry about polypharmacy or adjusting the loading dose
- Be Aggressive
  - Use higher than normal doses
  - Use evidence-based references rather than drug references
  - Use loading doses
- Monitor
  - Monitor AED levels
  - Monitor for side effects from the AED
- Individualize
  - Can use everything we know
  - Pick the drug that is most appropriate for the patient
    - Can do this up-front or when weaning AED off