

Important Tips in the Management of Epilepsy

Deepika Pereira, Pharm.D, BCPS
Neuro/Spine Critical Care Pharmacist
Northwestern Memorial Hospital

No conflicts of interest to disclose

Illinois Council of Health-System Pharmacists 2015 Annual Meeting

Learning Objectives for Pharmacists

- List treatment pearls for common issues related to the management of epilepsy in the hospital setting
- Describe alternative treatment options for epilepsy due to medication shortage issues in the hospital setting

Illinois Council of Health-System Pharmacists 2015 Annual Meeting

Learning Objectives for Pharmacy Technicians

- Recognize the impact of drug shortages on the management of epilepsy in the hospital setting
- List the available dosage forms of the anti-epileptic medications discussed during this presentation

Illinois Council of Health-System Pharmacists 2015 Annual Meeting

Epilepsy: Background

- Affects ~3 million people in the US each year
- 10% of Americans will experience a seizure sometime in their lives
- 3% will receive a diagnosis of epilepsy by age 80
- Encompasses different seizure types and syndromes
- Usually difficult to ascertain cause
- Idiopathic (unknown cause) vs symptomatic (secondary to an identifiable condition)

Illinois Council of Health-System Pharmacists 2015 Annual Meeting

Epilepsy: Definitions

- Seizures: disordered, synchronous and rhythmic firing of neurons thought to arise from the cerebral cortex
- Epilepsy: disorder of brain function characterized by the periodic and unpredictable occurrence of seizures

Illinois Council of Health-System Pharmacists 2015 Annual Meeting

Management of Epilepsy

- Medication management
 - First unprovoked seizure
 - Chronic epilepsy syndromes
 - Status epilepticus
- Surgery

Illinois Council of Health-System Pharmacists 2015 Annual Meeting

Medication management challenges

- Timing of medication administration
- Evidence based literature includes mostly expert opinion
- Extensive drug-drug interactions, short term and long term adverse effects, therapeutic drug monitoring
- Pharmacoresistance
- Drug shortages
- Education of healthcare providers

Illinois Council of Health-System Pharmacists 2015 Annual Meeting

Timing

- Status epilepticus (SE) is defined as 5 minutes or more of (i) continuous clinical and/or electrographic seizure activity or (ii) recurrent seizure activity without recovery between seizures
- “Animal data suggest that permanent neuronal injury and pharmacoresistance may occur before the traditional definition of 30 min of continuous seizure activity have passed”
- Control of SE should be achieved within 60 minutes of onset
- Refractory SE is defined as those patients who have failed first 2 anti-epileptic drugs (AEDs) administered
 - Consider use of continuous infusions

Illinois Council of Health-System Pharmacists 2015 Annual Meeting

Tips on timing

- No established intravenous access
 - Alternate routes of benzodiazepines
 - Rectal diazepam
 - Intramuscular (IM) midazolam
 - IM: 2 ml in the deltoid and thigh muscles, and up to 5 ml in the gluteus maximus
 - Fosphenytoin is not caustic
- Hemodynamically unstable patients
 - Use of fosphenytoin
 - Maximum rate: 150 mg/min

Illinois Council of Health-System Pharmacists 2015 Annual Meeting

Evidence-based support

Treatment	Class/level of evidence	References
Emergency treatment		
Lorazepam	Class I, level A	[19, 30, 52, 83, 87-93]
Midazolam	Class I, level A	[64, 99-106]
Diazepam	Class IIa, level A	[30, 87, 90, 95, 97-105, 107, 109-114]
Phenytoin/fosphenytoin	Class IIb, level A	[30, 87, 94, 115-119]
Propofol	Class IIb, level A	[30, 87, 114]
Valproate sodium	Class IIb, level A	[116, 117, 120-127]
Levetiracetam	Class IIb, level C	[119, 123-131]
Usual treatment		
Valproate sodium	Class IIa, level A	[117, 120-122, 131-134]
Phenytoin/fosphenytoin	Class IIa, level B	[30, 87, 97, 107, 114, 115, 117, 119, 132, 133, 137]
Midazolam (continuous infusion)	Class IIb, level B	[109]
Propofol	Class IIb, level C	[128, 129]
Levetiracetam	Class IIb, level C	[119, 123, 128-127, 126, 133, 140, 141]
Refractory treatment		
Midazolam	Class IIa, level B	[28, 106-108, 142-150]
Propofol	Class IIb, level B	[26, 28, 62, 66, 68, 144, 151-153]
Propofol/diazepam	Class IIa, level B	[26, 27, 29, 34, 39, 62, 63, 66, 68, 107, 115, 139, 154, 156-158]
Valproate sodium	Class IIa, level B	[128, 131, 134, 139, 150-153]
Levetiracetam	Class IIb, level C	[17, 66, 125-127, 129, 140, 141, 159, 163-164]
Phenytoin/fosphenytoin	Class IIb, level C	[57, 160]

Illinois Council of Health-System Pharmacists 2015 Annual Meeting

Evidence-based support

Seizure type or epilepsy syndrome	Class I studies	Class II studies	Class III studies	Level of efficacy and effectiveness evidence (in alphabetical order)
Adults with partial-onset seizures	4	1	34	Level A: CBZ, LEV, PHT, ZNS Level B: VPA Level C: GBP, LTG, QXG, PB, TPM, VGB Level D: GGT, PRM Level E: QXG Level S: None Level C: CBZ, PB, PHT, TPM, VPA, VGB Level D: CBZ, C, QXG, VTC, ZNS
Children with partial-onset seizures	1	0	19	Level A: None Level B: None Level C: CBZ Level D: TPM, VPA Level E: None Level A: None Level B: None Level C: None Level D: None Level E: None
Adults with generalized-onset tonic-clonic seizures	0	0	27	Level A: None Level B: None Level C: None Level D: None Level E: None Level A: None Level B: None Level C: None Level D: None Level E: None
Children with generalized-onset tonic-clonic seizures	0	0	14	Level A: None Level B: None Level C: None Level D: None Level E: None Level A: None Level B: None Level C: None Level D: None Level E: None
Children with absence seizures	1	0	7	Level A: None Level B: None Level C: None Level D: None Level E: None Level A: None Level B: None Level C: None Level D: None Level E: None
Benign epilepsy with centrotemporal spikes (BECTS)	0	0	3	Level A: None Level B: None Level C: None Level D: None Level E: None Level A: None Level B: None Level C: None Level D: None Level E: None
Juvenile myoclonic epilepsy (JME)	0	0	1	Level A: None Level B: None Level C: None Level D: None Level E: None Level A: None Level B: None Level C: None Level D: None Level E: None

Illinois Council of Health-System Pharmacists 2015 Annual Meeting

Evidence-based support

- SE guidelines include recommendations made from the results of an international survey and expert opinion
- International League Against Epilepsy updated review concluded that existing randomized controlled trials researching adult generalized tonic-clonic epilepsy are methodologically flawed and not adequate to answer important clinical questions

Illinois Council of Health-System Pharmacists 2015 Annual Meeting

Medication profiles

Drug	Metabolism	Half-life (hours)	Therapeutic drug monitoring	ADE	Dosage forms	Comments
Fosphenytoin	rapidly converted via hydrolysis to phenytoin	Conversion half-life: 15 minutes	Free phenytoin level: 1-2 Total phenytoin level: 10-20	Arrhythmias	IV: 50 mg PE/ml	Preferred use in hemodynamically unstable patients or those with inadequate IV access
Lacosamide	40% unchanged 30% O-desmethyl-LCM (CYP2C19)	13	None	PR prolongation	Oral: 50 mg, 100 mg, 150 mg, 200 mg tablets and 10 mg/ml solution IV: 10 mg/ml	Reduce dose in severe liver cirrhosis 50% supplemental dose after dialysis
Levetiracetam	66% excreted unchanged 24% hydrolyzed	7		Well tolerated	Oral (IR): 250 mg, 500 mg, 750 mg, 1000 mg and 100 mg/ml solution Oral (ER): 500 mg and 750 mg IV: 100 mg/ml	Renal dose adjustment Supplemental dose adjustments after dialysis
Lorazepam	Glucuronidation 75% of metabolite excreted in urine	14-18	None	Hypotension Respiratory depression	Oral: 0.5 mg, 1mg, 2 mg tablets and 2 mg/ml solution IV: 2 mg/ml and 4 mg/ml	Contains propylene glycol

Illinois Council of Health-System Pharmacists 2015 Annual Meeting

Drug	Metabolism	Half-life (hours)	Therapeutic drug monitoring	ADE	Dosage forms	Comments
Pentobarbital	Hydroxylated and then glucuronidated	15-50	5-20 mcg/ml	Respiratory depression Cardiac depression Paralytic ileus	IV: 50 mg/ml	Can mimic brain death Must be mechanically ventilated
Phenobarbital	50% hydroxylated, 25% glucuronidated 25% excreted unchanged	80-100	10-40 mcg/ml	Sedation Hypotension Respiratory depression	Oral: 20 mg/5ml solution 15 mg, 16.2 mg, 32.4 mg, 60 mg, 64.8 mg, 97.2 mg and 100 mg tablets IV: 65 mg/ml and 130 mg/ml	Sequential loading if hypotensive
Phenytoin	70% hydroxylated, then glucuronidated	20-60	Free phenytoin level: 1-2 Total phenytoin level: 10-20	Arrhythmias Hypotension Purple glove syndrome	Oral: 50 mg chew tabs, 30 mg and 100 mg ER capsules, 125 mg/ml solution IV: 50 mg/ml	Saturable pharmacokinetics Unpredictable levels in uremia
Valproate sodium	50% glucuronidated 50% multiple other pathways including beta-oxidation	9-16	Total valproate levels: 50-150 mcg/ml	Hyperammonemia Hepatotoxicity Thrombocytopenia	Oral: 125 mg sprinkle capsules, 250 mg and 500 mg ER tablets, 125mg, 250 mg and 500 mg DR tablets 250 mg IR capsules 250 mg/5 ml solution IV: 100 mg/ml	Preferred in anoxic brain injury Many formulations

Illinois Council of Health-System Pharmacists 2015 Annual Meeting

Pharmacoresistance

- Failure of adequate trials of two tolerated, appropriately chosen and administered antiepileptic drugs (whether as monotherapy or in combination) to achieve seizure freedom
- Likelihood of successful treatment with other drugs of different class diminishes

Illinois Council of Health-System Pharmacists 2015 Annual Meeting

Pharmacoresistance

- Alternative treatment options:
 - Combination medication therapy
 - Newer agents: eslicarbazepine and perampanel
 - Ketogenic diet
 - Rapid cooling
 - Herbal: ginger, ginseng, ginkgo biloba, kava kava, marijuana, melatonin, St. John's wort, valerian

Illinois Council of Health-System Pharmacists 2015 Annual Meeting

Drug shortages

- Defined as a supply issue that affects how the pharmacy prepares or dispenses a drug product or influences patient care when prescribers must use an alternative when prescribers must use an alternative agent

Illinois Council of Health-System Pharmacists 2015 Annual Meeting

Current Shortages

Drug Name	Shortage date	Reason
Divalproex sodium tablets	June 8, 2015	Product discontinued, manufacturer delay, on allocation
Levetiracetam injection	July 22, 2015	Manufacturer delay, increased demand
Lorazepam injection	July 16, 2015	Product discontinued, increased demand
Valproate sodium injection	August 11, 2015	Manufacturer delay

Illinois Council of Health-System Pharmacists 2015 Annual Meeting

Resolved Shortages

Drug Name	Date resolved
Diazepam injection	October 4, 2013
Fosphenytoin injection	April 2, 2015
Ketamine injection	October 23, 2014
Midazolam injection	August 6, 2015
Phenobarbital injection and tablets	October 19, 2011 and May 8, 2014
Phenytoin injection and oral	January 23, 2015 and October 4, 2011
Propofol injection	January 19, 2014
Topiramate capsules	August 10, 2011
Topiramate sprinkle capsules	April 23, 2014

Illinois Council of Health-System Pharmacists 2015 Annual Meeting

Alternative treatment options

- Evidence based literature

Treatment	Class/level of evidence	References
Emergency treatment		
Lorazepam	Class I, level A	[19, 30, 57, 83, 87-90]
Midazolam	Class I, level A	[84, 99-108]
Diazepam	Class IIa, level A	[30, 87, 90, 95, 97-105, 107, 109-114]
Phenytoin/fosphenytoin	Class IIb, level A	[30, 87, 94, 115-119]
Phenobarbital	Class IIb, level A	[30, 87, 114]
Valproate sodium	Class IIb, level A	[116, 117, 130-132]
Levetiracetam	Class IIb, level C	[119, 135-136]
Usual treatment		
Valproate sodium	Class IIa, level A	[117, 120-122, 131-130]
Phenytoin/fosphenytoin	Class IIa, level B	[30, 87, 97, 107, 114, 115, 117, 119, 132, 133, 137]
Midazolam (continuous infusion)	Class IIb, level B	[106]
Phenobarbital	Class IIb, level C	[138, 139]
Levetiracetam	Class IIb, level C	[119, 123, 125-127, 129, 133, 140, 141]
Refractory treatment		
Midazolam	Class IIa, level B	[28, 106-108, 142-140]
Propofol	Class IIb, level B	[26, 36, 62, 86, 88, 114, 151-155]
Propofol/alfentanil	Class IIb, level B	[26, 27, 56, 58, 59, 62, 63, 66, 68, 107, 115, 139, 154, 156-158]
Valproate sodium	Class IIa, level B	[120, 121, 131, 126, 159-161]
Levetiracetam	Class IIb, level C	[37, 66, 135-137, 159, 140, 141, 159, 165-164]
Phenytoin/fosphenytoin	Class IIb, level C	[57, 165]

Illinois Council of Health-System Pharmacists 2015 Annual Meeting

- ### Alternative treatment options
- Use different agents within the same class
 - Benzodiazepines
 - Barbiturates
 - Phenytoin versus fosphenytoin
- Illinois Council of Health-System Pharmacists 2015 Annual Meeting

- ### Alternative treatment options
- Use different dosage forms
 - Oral loading: phenytoin
 - Maximum absorption= 400 mg
 - Switch from oral solutions to tablets or capsules
 - dose based on drug delivery of formulation
- Illinois Council of Health-System Pharmacists 2015 Annual Meeting

Alternative treatment options

- Use agents with similar mechanism of action

Drug Name	Sodium channel	Calcium channel	GABA
Benzodiazepines			++
Carbamazepine	++	+	
Lacosamide	++		
*Lamotrigine	++	+	
Levetiracetam		+	
Oxcarbazepine	++	+	
Phenobarbital			++
Phenytoin	++		
*Topiramate	+	+	+
*Valproate	+	+	+

*Broad spectrum

Illinois Council of Health-System Pharmacists 2015 Annual Meeting

- ### Summary
- Management of epilepsy is complex and challenging
 - No established guideline or literature to support the use of one AED over another
 - guidelines exist for the treatment of status epilepticus
 - Pharmacists and technicians can make an impact in assisting healthcare providers with alternatives in the setting of drug shortages.
- Illinois Council of Health-System Pharmacists 2015 Annual Meeting

CW is a 20 year old female who presents to the emergency department after a generalized tonic-clonic seizure and brief loss of consciousness. She is alert and oriented currently and able to tell you that she has never had a seizure before and she has been very stressed lately with finals. She has been pulling consecutive all nighters and consuming 2 pots of coffee each day.

How would you treat CW?

- A. Initiate phenytoin 15 mg/kg loading dose and 100 mg PO TID
- B. Do not initiate any medication at this time
- C. Administer lorazepam 2 mg IV push and send CW home
- D. Initiate midazolam infusion

Illinois Council of Health-System Pharmacists 2015 Annual Meeting

The guidelines for the management of status epilepticus includes:

- A. Only Class I, level A evidence based recommendations
- B. Only expert opinion
- C. Some expert opinion and some Class I, level A evidence
- D. Evidence that cannot be interpreted

Illinois Council of Health-System Pharmacists 2015 Annual Meeting

A patient is noted to have status epilepticus on electroencephalogram (EEG) monitoring but has lost IV access and the physician would like to administer medication to break the seizure now.

What medication could you provide?

- A. Rectal diazepam 0.2 mg/kg
- B. Rectal midazolam 0.2 mg/kg
- C. Intramuscular diazepam 0.15 mg/kg
- D. Phenytoin oral loading dose 15 mg/kg

Illinois Council of Health-System Pharmacists 2015 Annual Meeting

Pharmacoresistance is a prevalent issue in managing epilepsy. What alternative treatment option is recommended to overcome pharmacoresistance?

- A. Herbal supplements
- B. Electroconvulsive therapy
- C. Combining AEDs with differing mechanisms of action
- D. Warming

Illinois Council of Health-System Pharmacists 2015 Annual Meeting

Valproate sodium injection is on short supply. A patient has been on 500 mg IV infusion every 6 hours and needs to be converted to an oral formulation. What dosing would be equivalent?

- A. Divalproex sodium 500 mg DR PO twice a day
- B. Divalproex sodium 1500 mg ER PO once daily
- C. Divalproex sodium 500 mg DR PO every 6 hours
- D. Valproic acid oral solution 500 mg PO every 6 hours

Illinois Council of Health-System Pharmacists 2015 Annual Meeting

References

1. Epilepsy Foundation. Epilepsy Statistics. Available at: <http://www.epilepsy.com/learn/epilepsy-statistics>. Accessed August 20, 2015
2. Institute of Medicine Report. Epilepsy Across the Spectrum: Promoting Health and Understanding. Available at: http://iom.nationalacademies.org/-/media/Files/Report%20Files/2012/Epilepsy/epilepsy_slides.pdf. Accessed August 20, 2015
3. McNamara JO. Chapter 21. Pharmacotherapy of the Epilepsies. In: Brunton LL, Chabner BA, Knollmann BC, eds. Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12e. New York, NY: McGraw-Hill; 2011. <http://accessmedicine.mhmedical.com.ezproxy.galter.northwestern.edu/content.aspx?bookid=3748&Sectionid=41296227>. Accessed August 20, 2015.
4. Brophy GM, Bell R, Claassen J et al. Neurocritical Care Society Status Epilepticus Guideline Writing Committee. Guidelines for the evaluation and management of status epilepticus. Neurocrit Care. 2012 Aug;17(1):3-23
5. Krumholz A, Welte S, Gronseth GS et al. Evidence-based guideline: Management of an unprovoked first seizure in adults. Neurology. 2015;84:1705-1713
6. Glauser T, Ben-Menachem E, Bourgeois B, et al. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. Epilepsia. 2013 54(3):551-563.
7. Kwan P, Arzamanoglou A, Berg AT et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia. 2010; 51(6):1069
8. Kwan P, Schachter SC, Brodie MJ. Drug-Resistant Epilepsy. N Engl J Med 2011; 365:919-926
9. Sharma AK, Rani E, Wahsed A et al. Pharmacoresistant Epilepsy: A Current Update on Non-Conventional Pharmacological and Non-Pharmacological Interventions. J Epilepsy Res. 2015; 5(1); 2015
10. Fox E, Birt A, James K, Kolkko H, et al. ASHP guidelines on managing drug product shortages in hospitals and health systems. Am J Health-Syst Pharm. 2009; 66:1399-406
11. American Society of Health-Systems Pharmacists. Drug Shortages: Current Drugs. Available at: <http://www.ashp.org/drugshortages/current/>. Accessed August 20, 2015

Illinois Council of Health-System Pharmacists 2015 Annual Meeting