

# Antiepileptic for Seizure Prophylaxis in Traumatic Brain Injury Patients

Nattapol Malison, Pharm.D., BCPS, FACP<sup>1</sup>



Nattapol Malison, Pharm.D.,  
BCPS, FACP

## Abstract

Antiepileptic drugs should be considered to prevent early posttraumatic seizure (PTS) in patients with moderate or severe traumatic brain injury (TBI). Evidence shows that antiepileptic drugs do not reduce the risk of late PTS. The recommended first line antiepileptic drugs for PTS prophylaxis is intravenous phenytoin with a loading dose of 20 mg/kg, followed by a maintenance dose to achieve a serum Phenytoin level at 10-20 mg/L. The patient should be closely monitored for responses to the medication and side effects. Levetiracetam which has equal efficacy may be considered in patients who cannot tolerate Phenytoin. However, the cost of Levetiracetam may be higher. Valproic acid may be considered in case of limited resources. Carbamazepine can be an option when all previously mentioned drugs cannot be used. Determining an individualized dosage regimen and monitoring plan is required during the course of treatment.

**Keywords :** antiepileptic, seizure prophylaxis, traumatic brain injury, posttraumatic seizure

<sup>1</sup> Clinical Pharmacy Department, Bangkok Hospital, Bangkok, Thailand.

**B**rain injury (head injury, traumatic brain injury; TBI) refers to injuries caused by external impact to the brain resulting in the structural brain damage or deterioration of brain function. The worldwide incidence rate of TBI has been rising each year due to the increasing number of vehicles in developing countries. Transport accidents, a common source of TBI, cause injury and disability to 20-50 million people and cause death to more than 1.2 million people each year globally. This issue has significantly impacted the world's economy with 1-2% of gross national product (GNP) or up to \$ 518 billion per year has been attributed as damage and loss caused by accidents worldwide.<sup>1</sup>

According to Thailand's public health statistics for 2015, the mortality rate from transport accidents is at 22.3 per 100,000 population, which is the 5th most common cause of death for Thai population, preceded by cancer, strokes, pneumonia, and cardiovascular diseases, respectively. The rate of hospitalization for brain injuries is approximately 120 per 100,000 population.<sup>2</sup>

TBI can be classified into three levels, based on severity of impact using the Glasgow Coma Scale (GCS): mild TBI (GCS 13-15), moderate TBI (GCS 9-12) and severe TBI (GCS 3-8).<sup>1,3,4</sup> 70-90% of patients in Thailand are classified as mild TBI.<sup>1</sup>

The mechanisms of TBI can be divided into two categories: the primary and the secondary injuries. The primary injury is the focal or diffuse injury or cell death as a direct result of an accident. The secondary injury, which is the damage of neurons caused by a primary injury such as brain ischemia, metabolism and immune system disorder, inflammation of the brain tissue, and seizure.<sup>3,4</sup>

\* Address Correspondence to author:  
Nattapol Malison, Pharm.D., BCPS, FACP  
Clinical Pharmacy Department, Bangkok  
Hospital, 2 soi Soonvijai 7, New Petchburi Rd.,  
Bangkok, 10310, Thailand.  
email: [bmclinicalphar@bgh.co.th](mailto:bmclinicalphar@bgh.co.th)  
[natt\\_2528@hotmail.com](mailto:natt_2528@hotmail.com)

Received: May 22, 2017  
Revision received: May 23, 2017  
Accepted after revision: June 14, 2017  
BKK Med J 2017;13(2): 87-90  
[www.bangkokmedjournal.com](http://www.bangkokmedjournal.com)

**Posttraumatic seizure (PTS)** occurs by multiple mechanisms including tearing, bruising, scarring or bleeding in the brain; toxicity of hemoglobin breakdown products; and diffuse axonal injury. Incident rates of PTS ranged from 5-50% because of variations in seizure measurement, sample size, and setting of study. PTS may cause secondary brain injury because of increased metabolic demands, increased intracranial pressure, compromised cerebral oxygen delivery, and excess neurotransmitter release.<sup>5</sup> PTS is classified by onset of a seizure.<sup>3-6</sup>

1. **Early posttraumatic seizure (Early PTS)** is a seizure that occurs during the first week after injury. Early PTS is caused by new gene transcription and changes in receptor proteins and ion channels. This occurs in approximately 4-25% of cases, if not prevented.
2. **Late posttraumatic seizure (Late PTS)** is a seizure that occurs after the first week of the injury. Late PTS is caused by changes in the structure of nerve cells in the area damaged by the injury. This occurs in approximately 9-42% of cases, if not protected.

Patients who are at risk for PTS include patients with a GCS  $\leq 10$ , patients with immediate seizures, patients who have posttraumatic amnesia lasting longer than 30 minutes, patients with linear or depressed skull fracture, patients who suffer penetrating head injury, patients with subdural or epidural or intracerebral hematoma, patients with cortical contusion, patients aged  $\leq 65$  years old and patients with chronic alcoholism.<sup>3,5,6</sup>

In addition, if a patient has recurrent seizures for more than 7 days following injury, the condition is called posttraumatic epilepsy (PTE). Patients who are at risk for PTE are individuals who have suffered the following: severe TBI patients who had early PTS prior to discharge; acute intracerebral hematoma or cortical contusion; posttraumatic amnesia lasting longer than 24 hours; age 65 years old or older; or premorbid history of depression.<sup>6</sup>

**Use of antiepileptic drugs for PTS prophylaxis after TBI** is crucial. It not only reduces the incidence of seizures but also prevents complications of TBI such as herniation, abnormalities in brain physiology, chronic seizures and death. Therefore effective antiepileptic drugs with fewer side effects should be considered for seizure prophylaxis. Findings from a meta-analysis by Thompson K.,<sup>7</sup> and colleagues showed that antiepileptic drugs prevent early PTS (risk ratio 0.42 [95% CI: 0.23-0.73]) but not late PTS or death from TBI. Adverse event rates were not different between patients using antiepileptic drugs and patients using placebo.<sup>7</sup> Guidelines for the Management of Severe Traumatic Brain Injury 4<sup>th</sup> edition issued by the Brain Trauma Foundation in 2016 and the American Society of Health-System Pharmacists in 2013 recommends PTS prophylaxis only during the first seven days after TBI, especially if risk factors for early PTS are present. There has been no conclusive evidence to support PTS prophylaxis for longer than seven days after TBI, even if risk factors are present.<sup>3,6</sup>

**Phenytoin is the first line of antiepileptic drugs recommended** for early PTS prophylaxis.<sup>3,5,6</sup> Phenytoin has been used to prevent seizures in TBI patients for decades. A randomized, controlled trial study conducted by Temkin NR and colleagues<sup>8</sup> in 1990 compared the use of phenytoin and placebo in 404 moderate to severe TBI patients for PTS prevention. Findings showed that patients who received a loading dose of 20 mg/kg phenytoin within 24 hours after injury and a maintenance dose that achieved a serum phenytoin level at 10-20 mg/dL had lower rates of early PTS. (Cumulative seizure rate in patients receiving phenytoin = 3.6, patients receiving placebo = 14.2; risk ratio 0.27 (95% CI: 0.12-0.62),  $p < 0.001$ ). However, the rate of late PTS and death were not different between the two groups. Medication-related adverse events at the first and second weeks of treatment were also not different between the treatment and the control group.<sup>3,4,6</sup> The recommended dosage of phenytoin for PTS prophylaxis in TBI patients is based on the previously mentioned study which is a loading dose of 20 mg/kg intravenously at the rate of less than 50 mg/min, then followed by a maintenance dose of 300 mg/day or 4-7 mg/kg/day to achieve a serum Phenytoin level at 10-20 mg/L. Phenytoin requires close therapeutic drug monitoring due to its dose-related adverse events. Unique pharmacokinetic properties of phenytoin such as extensive plasma protein binding (90-95%), saturation of metabolism, non-linear elimination kinetics all affect phenytoin drug levels. Phenytoin is primarily metabolized by cytochrome P450 CYP2C9 (70-90%) and it induces cytochrome P450 CYP2C9 and CYP3A4, P-glycoprotein, and UGT1A1. Phenytoin may interact with other drugs and alter the effect of drugs such as anticoagulants. Higher serum concentrations of phenytoin were measured in patients with the CYP2C9\*3 genotype. A standard Phenytoin dose is associated with serious toxicity in TBI patients with the CYP2C9\*3 genotype, so a lower dose of phenytoin dose is required. In addition, the condition of TBI patients using phenytoin should be taken into consideration because it could alter the required phenytoin drug level. Patients with TBI are critically ill, and therefore any physiological changes such as liver impairment, kidney impairment, low serum albumin, hypermetabolic state, high-protein intakes, cytokines release (Interleukin-6), and change in blood-brain barrier function could impact the pharmacokinetic properties of phenytoin. These conditions may influence the serum phenytoin level and the patient's response to the medication. Therefore, pharmacists and healthcare professionals should systematically evaluate and monitor serum phenytoin levels, patient's response to treatment, as well as adverse events.<sup>3,9</sup> Common adverse events in the first week of Phenytoin treatment include drowsiness, rash, injection site reaction, hypotension, and elevation of liver enzyme levels.<sup>3,8</sup>

**Alternative antiepileptic drugs for PTS prophylaxis** include Levetiracetam,<sup>3,5,6</sup> Valproic acid,<sup>3,4,6</sup> and Carbamazepine.<sup>3,4,16</sup>

**Levetiracetam** is a new antiepileptic drug. Compared to Phenytoin, Levetiracetam has low plasma protein binding, lower risk of drug-interactions and adverse events. Levetiracetam major metabolic pathway is hydrolysis, not the CYP450 enzyme. However, the drug is eliminated via the kidney, so patients who are critically ill or suffer from renal insufficiency may require dosage adjustment. Therapeutic drug monitoring may be required in complicated cases.<sup>3,10,11</sup> Efficacy of Levetiracetam in PTS prophylaxis is not different from Phenytoin.

A meta-analysis by Zafar SN and colleagues<sup>10</sup> in 2011, comparing Levetiracetam and Phenytoin in PTS prophylaxis for TBI patients showed no statistically significant difference in preventing early PTS or late PTS. Inaba K and colleagues<sup>12</sup> conducted a prospective multicenter study in 2013 comparing Levetiracetam in the dose of 1000 mg intravenously administered every 12 hours to the recommended dose of Phenytoin for 7 days in PTS prophylaxis in TBI patients. The result showed no statistically significant difference in the seizure rate within the 7-days of treatment (Levetiracetam = 1.5% and Phenytoin = 1.5%,  $p = 0.997$ ), incidence of adverse events (7.9% and 10.3%,  $p = 0.227$ ), or mortality rates (5.4% and 3.7%,  $p = 0.236$ ). Another recent study conducted in a single-center by Gabriel WM and Rowe AS<sup>13</sup> in 2014, compared efficacy and safety of these two medications for long-term use at a period of six months after TBI. No difference was found in the Glasgow Outcome Scale-Extended (GOS-E) score. However, the group receiving Phenytoin reported to have fever while taking the medication, but there was no such symptom in the group receiving Levetiracetam. A few side effects associated with Levetiracetam include headache, nausea, vomiting, drowsiness, dizziness and behavioral changes.<sup>10</sup>

Although Levetiracetam has an equivalent clinical efficacy in PTS prophylaxis among TBI patients, Levetiracetam is not considered the first line therapy because of its cost. The cost-minimization analysis of Levetiracetam versus phenytoin in PTS prophylaxis showed that Phenytoin is less expensive than Levetiracetam from both the institution (phenytoin = \$ 151.24 and levetiracetam = \$ 411.85 per person) and patient (phenytoin = \$ 2,302.58 and Levetiracetam = \$ 3,498.40 per person) perspectives.<sup>14</sup> Cost-utility analysis showed that the cost of Phenytoin is \$1.58 per quality-adjusted life years (QALY) and Levetiracetam is at \$20.72 per QALY. In addition, sensitivity analysis showed that Levetiracetam would be more cost-effective than Phenytoin, if Levetiracetam provides 100% prevention against early PTS with the cost of less than \$400 for 7-day dosage. Therefore, using phenytoin to prevent early PTS is a better economic option compared to Levetiracetam.<sup>10,15</sup> When generic Levetiracetam becomes available on the market,

the total cost of Levetiracetam for PTS prophylaxis will be much cheaper. A revised cost evaluation study is needed.

**Valproic acid** has a limited use for PTS prophylaxis in TBI patients. A randomized, double-blinded trial by Temkin NR and colleagues in 1999 compared the efficacy of valproic acid which was started within 24 hours after injury at the dose of 20 mg/kg by intravenous injection, followed by 15 mg/kg/day divided into four times a day to achieve the serum valproic acid level at 40-100 mg/L to the standard of Phenytoin. The result showed no significant difference in the rate of early PTS between the two groups (relative risk 2.9; 95% CI 0.7-13.3). No differences were detected between patients who received placebo and patient who received valproic acid in a period of 1 or 6 months. However, there was a trend toward higher mortality in patients treated with valproic acid.<sup>6,16</sup> Further analysis on neuropsychological function at 1, 6, and 12 months after TBI showed that no beneficial or adverse events of valproic acid were found compared with phenytoin or placebo.<sup>6</sup> Therefore, with inadequate data and higher potential for mortality, valproic acid has limited use for preventing seizures in TBI patients.<sup>3,4,6</sup>

**Carbamazepine:** One study was conducted using carbamazepine to prevent seizures in severe TBI patients. The dosage used in the study is started at 100 mg three times a day and followed by maintaining a serum therapeutic level (4-12 mg/L) for 1.5-2 years. The study found that carbamazepine reduced the rate of early PTS by 61% when compared with placebo (P value <0.05) and reduced the rate of late PTS by 20%. However, these data are derived from a single study and were not compared to the standard regimen. Carbamazepine is an alternative option when other medication cannot be used.<sup>3,4,17</sup>

## Conclusion

Antiepileptic drugs are recommended for early PTS prophylaxis in patients with moderate to severe TBI. Evidence shows that antiepileptic drugs do not reduce the risk of late PTS. Phenytoin is the recommended first line antiepileptic drug for early PTS prophylaxis in patients with moderate to severe TBI. Dosage monitoring and close monitoring of serum phenytoin levels is required in order to prevent dose-related adverse events. Second line therapy of PTS prophylaxis is Levetiracetam because it has equal efficacy to Phenytoin but it is costlier. Intravenous administration of antiepileptic drugs is preferred in critically-ill patients. Valproic acid and carbamazepine may be considered in case of Phenytoin intolerance.

## References

1. Panjaisee S, Peunpatom N, Weerasarn K. Clinical Practice Guidelines for Traumatic Brain Injury (1<sup>st</sup> edition). Bangkok: Thana Press. 2013:1-2.
2. Bureau of Policy and Strategy Ministry of Public Health. Public Health Statistics A.D. 2015. (Accessed Dec 26, 2016 at [http://bps.moph.go.th/new\\_bps/sites/default/files/health\\_statistic2558.pdf](http://bps.moph.go.th/new_bps/sites/default/files/health_statistic2558.pdf).)

3. Torbic H, Forni AA, Anger KE, et al. Use of antiepileptics for seizure prophylaxis after traumatic brain injury. *Am J Health-Syst Pharm* 2013; 70: 759-66.
4. Algattas H, Huang JH. Traumatic brain injury pathophysiology and treatments: early, intermediate, and late phases post-injury. *Int J Mol Sci* 2014;15:309-41.
5. The Department of Surgical Education, Orlando Regional Medical Center. Seizure prophylaxis in patients with traumatic brain injury. 2012. (Assessed Dec 26, 2016 at <http://www.surgicalcriticalcare.net/Guidelines/Seizure%20prophylaxis%20in%20TBI.pdf>.)
6. Brain Trauma Foundation. Guidelines for the management of severe traumatic brain injury 4th edition. 2016:120-9. (Assessed Dec 26, 2016 at [https://braintrauma.org/uploads/03/12/Guidelines\\_for\\_Management\\_of\\_Severe\\_TBI\\_4th\\_Edition.pdf](https://braintrauma.org/uploads/03/12/Guidelines_for_Management_of_Severe_TBI_4th_Edition.pdf).)
7. Thompson K, Pohlmann-Eden B, Campbell LA, et al. Pharmacological treatments for preventing epilepsy following traumatic head injury. *Cochrane Database Syst Rev* 2015;8:1-83.
8. Temkin NR, Dikmen SS, Wilensky AJ, et al. A randomized, double-blind study of Phenytoin for the prevention of post-traumatic seizures. *N Engl J Med* 1990;323(8):497-502.
9. Freund V, Chetty M. Dosing and therapeutic monitoring of phenytoin in young adults after neurotrauma: are current practices relevant? *Clin Neuropharmacol* 2007;30:362-9.
10. Zafar SN, Khan AA, Ghauri AA, et al. Phenytoin versus Levetiracetam for seizure prophylaxis after brain injury - a meta-analysis. *BMC Neurol* 2012;12(30):1-8.
11. Nau KM, Divertie GD, Valentino AK, et al. Safety and efficacy of Levetiracetam for critically ill patients with seizures. *Neurocrit Care* 2009;11:34-7.
12. Inaba K, Menaker J, Branco BC, et al. A prospective multicenter comparison of Levetiracetam versus Phenytoin for early posttraumatic seizure prophylaxis. *J Trauma Acute Care Surg* 2013; 74(3):766-73.
13. Gabriel WM, Rowe AS. Long-term comparison of GOS-E scores in patients treated with Phenytoin or Levetiracetam for posttraumatic seizure prophylaxis after traumatic brain injury. *Ann Pharmacother* 2014;48(11):1440-4.
14. Pieracci FM, Moore EE, BeauchampK, et al. A cost-minimization analysis of Phenytoin versus Levetiracetam for early seizure pharmacoprophylaxis after traumatic brain injury. *J Trauma* 2012;72: 276-81.
15. Cottin BA, Kao LS, Kozar R, et al. Cost-utility analysis of Levetiracetam and Phenytoin for posttraumatic seizure prophylaxis. *J Trauma* 2011;71:375-9.
16. Temkin NR, Dikmen SS, Anderson GD, et al. Valproate therapy for prevention of posttraumatic seizures: a randomized trial. *J Neurosurg* 1999;91(4):593-600.
17. Glötzner FL, Haubitz I, Miltner F, et al. Seizure prevention using carbamazepine following severe brain injuries. *Neurochirurgia* 1983;26(3):66-79.