Comparative Study between Leviteracetam, Phenytoin & Carbamazepine in Treating Post Traumatic Epilepsy

Dr. Rana Hani Mohammed Ali Al-Shaikh Hamed[1*], Dr. Raad Ahmed Hussein[2], Sadoon A. Ibraheem[3], Dr. Muhammed Hameed Faeadh Al Jumaily[4]

Abstract

Aim: Evaluation of the advantages of Levetiracetam over Phenytoin & Carbamazepine in treatment of late post traumatic epilepsy.
Objectives: To compare between the effectiveness of antiepileptic drugs leviteracetam, phenytoin & carbamazepine in management of post-traumatic epilepsy.
Methods: This is a retrospective study on the medical treatment of 60 patients with post traumatic epilepsy. 20 patients of them were treated by leviteracetam, 20 patients by Tegretol, & 20 patients by phenytoin. Data was collected between January 2014 and January 2020 from the neurosurgical hospital in Baghdad. Patient demographics, aetiopathology, effectiveness & side effects were recorded.
Results: All the 60 patients with Post traumatic epilepsy were recorded.
Regarding the Aetiology: Brain CT scan demonstrated that 35 patients had brain cortical contusions, in 15 patients there were depressed skull fractures and 10 patients had acute subdural haemorrhage. All patients with depressed skull fractures & 8 patients wit subdural haematoma were treated surgically then medically. All the patients were treated with antiepileptic medications, so that 20 patients were treated with phenytoin, 20 patients with levetiracetam & 20 patients with carbamazepine.
Conclusions: Levetiracetam (Keppra) is a broad-spectrum antiepileptic drug with low incidence of cognitive problems. It is not metabolized in the liver. It has advantage over Phenytoin & Carbamazepine in management of post traumatic epilepsy due to fewer side effects.

Key Words: Post-traumatic Epilepsy, Levitracetam, Phenytoen, Carbamezepine.
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Introduction

Seizures are usual complication of Head injury. Early post head trauma seizures within the first week are regarded as acute symptomatic events, late post head trauma seizures after the first week regarded as late post traumatic epilepsy. Brain injury is common cause of symptomatic epilepsy between 15 and 24 years. Post head injury epilepsy contributes to the disability in a head injury survivor. **(1)** Post-traumatic epilepsy may occur even more than 15 years later. **(2,3,4,5,6) S**evere head injury has risk of development of late seizures. **(5)** Levetiracetam (Keppra) is a broad-spectrum antiepileptic drug with low incidence of cognetive dysfunction.

Corresponding author: Dr. Rana Hani Mohammed Ali Al-Shaikh Hamed
Address: [1*]B.Sc. Pharmacy, Master in Pharmaceutical Science, PhD in Pharmaceutical Science, Department of Pharmacology, College of Medicine, Aliraqia University; [2]M.B.Ch.B., F.I.B.M.S. Neuromedicine, Neurology Unit, Department of Internal Medicine, College of Medicine, Aliraqia University; [3]Assistant Professor, F. I. C. M. S. Occupational and Environmental Medicine, College of Medicine, Al_Iraqia University; [4]M.B.Ch.B., F.I.B.M.S. Neurosurgery, Neurosurgery Unit, Department of Surgery, College of Medicine, Aliraqia University.
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It is not metabolized in the liver. Common side effects are irritability, dizziness, insomnia, and mood changes. The **L**evetiracetam action is by binding to synaptic vesicle protein 2A (SV2A). SV2A is a membrane-bound protein on synaptic vesicles, it play a role in synaptic transmission. Stimulation of pre-synaptic SV2A by levetiracetam may inhibit neurotransmitter release**. (7,8,9)** The drug is excreted in urine without drug interactions. Levetiracetam can cause mood alterations**. (7)** Levetiracetam inhibit N-type calcium channels.**(10)** The adult dose is 500 - 1500 mg twice a day.**(11)** The drug does not require serum level monitoring. Adverse effects include dizziness, weakness & behavioral changes rarely.**(13)** Carbamazepine (Tegretol, Carbatrol) blocks sodium channels. Tegretol Side effects include sedation, dizziness, vertigo, diplopia, ataxia, GI upset, blurred vision, low blood counts & hyponatremia. Carbamazepine causes sometimes Stevens-Johnson syndrome. Acute intoxication causes coma & convulsion. Typical adult dose is 400 mg tid.**(13)** Phenytoin (Dilantin) stabilize neuronal membrane by inactivate voltage sensitive Na channels. Also it reduce Ca influx, inhibit glutamate and facilitate GABA response. Phenytoin adverse effects are gum hypertrophy, hirsutism, acne, hypersensitivity rash, lymphadenopathy, megaloblastic anaemia (folate deficiency), osteomalacia, hyperglycaemia, and in pregnancy: fetal teratogenic effect, hypoplastic phalanges, cleft palate & microcephaly. Cerebellar ataxia & vestibular dysfunction, vertigo, nystagmus, hallucination mental confusion, & behavioral alteration with cardiac arrhythmia by intravenous use. **(13)**

Patients & Methods

This is a retrospective study to compare the efficiency of 3 commonly used antiepileptic drugs (Leviteracetam, Phenytoin & carbamazepine). Our Data were collected between Mai 2014 & Mai 2020 from the neurosurgical hospital in Baghdad. They were 60 patients with post-traumatic epilepsy, 15 patients were females & 45 patients were males, 16 patients were children between 5-15 years, 42 patients were adults between 15-60 years & 2 patients older than 60 years. Brain CT scan demonstrated that 35 patients had brain cortical contusions, in 15 patients there were depressed skull fracture & 10 patients had acute subdural haemorrhage. Of those patients with post-traumatic epilepsy, 20 patients were treated with Levitracetam, 20 patients with Phenytoin & 20 patients with carbamazepine.

Results

Brain CT scan has been done for all patients, In 35 patients there were brain cortical contusions, in 15 patients there were depressed skull fractures & 10 patients had acute subdural haemorrhage. All patients with depressed skull fractures treated surgically with wound excision & debridement, craniectomy & dural tear repair. For the patients with acute subdural haematoma, 8 patients were treated surgically & 2 conservatively. All the patients were treated with antiepileptic medications, 20 patients were treated with phenytoin, 20 patients with levetiracetam & 20 patients with carbamazepine. In Levetiracetam group, good response to treatment was achieved based on glascow outcome scale score, 5 patients developed side effect of thrombocytopenia and headache versus 11 of 20 patients in Phenytoin group who developed cardiovascular tocxicity with arrhythmia and megaloblastic anaemia due to folate defeciency and hepatotocicity, and versus 9 of 20 patients who developed skin rash and SIADH with hyponatraemia in carbamazepine group.

Table 1. Demonstrated gender & age distribution of the patients

	5-15 years	15-60 years	More 60 years	Total
male	14	30	1	45
female	2	12	1	15
Total	16	42	2	60

Discussion

Epilepsy after traumatic brain injury (TBI) either early onset within the first week or late onset epilepsy after one week. Seizures after one week from head injury reflect permanent brain structural and physiologic changes and usually represent post-traumatic epilepsy onset. Levetiracetam (trade name: keppra) is effective antiepileptic drug in treatment of generalized tonic-clonic seizures, partial and myoclonic seizures. Leviteracetam side effects is more in old age group. It is safely used in children older than 4 years. The Mechanism of action of levetiracetam does not inhibit voltage-dependent Na+ channels, and not affect GABAergic transmission, and does not bind to GABAergic or glutamatergic receptors. It is neuromodulator binds to SV2A glycoprotein, and inhibits presynaptic calcium channels, to reduce

neurotransmitter. Levetiracetam has mild neuropsychiatric adverse effect including agitation, anxiety, emotional lability, hostility, and depression. More severe psychosis like Hallucinations, and suicide, are rare and occur within the first month of therapy. Toxic epidermal necrolysis and Stevens–Johnson syndrome are rare. Levetiracetam is contraindicated in hypersensitivity reactions against levetiracetam including unexplained rash, difficulty breathing, and chest tightness. It increase suicide or thoughts of suicide and worsen depression with alteration in emotional and behavioral conditionsconditions. Renal failure decreases elimination of levetiracetam. Therefore patients with renal failure need dose adjustments. Phenytoin (Dilantin) is effective anti-epileptic drug, useful for the prevention of tonic-clonic, complex partial and focal seizures. It is very effective against status epilepticus not responding to benzodiazepines. It is indicated also in heart arrhythmias and neuropathic pain. It is used also in Trigeminal neuralgia. Phenytoin has Narrow therapeutic index (10–20 μg/mL) It is contraindicated in Pregnancy because risk of fetal (hydantoin syndrome and bleeding). Phenytoin act by blocking voltage gated sodium channels, so reducing the action potentials. It inhibit the motor cortex seizure activity and stabilize hyperexcitability threshold and reduces the brain stem activity of the generalized tonic-clonic seizures. Phenytoin can cause gastric upset, anorexia, itching and rash, exfoliative dermatitis, hirsutism, gums hypertrophy, Hypertrichosis, Stevens– Johnson syndrome, drug-induced lupus, bone marrow suppression, and toxic epidermal necrolysis. It is teratogenic drug and can cause fetal cleft lip and palate. Phenytoin can cause also tremor, incoordination and nystagmus, double vision, slurred speech and cerebellar ataxia. It interfere with folate metabolism and cause megaloblastic anaemia, agranulocytosis and thrombocytopenia. Phenytoin increase suicide risk and worsen depression. It leads to Vitamin D deficiency, and low calcium and phosphate in the blood with osteoporosis. Carbamazepine (Tegretol) is antiepileptic drug and used also in neuropathic pain. It is effective in focal and generalized seizures but not in absence and myoclonic seizures. Carbamazepine action is by blocking sodium channel (voltage-gated sodium channels) and prevents action potential. Adverse effects include drowsiness, headaches, incoordination, aplastic anemia and agranulocytosis, hyponatremia due to SIADH, fetal congenital malformations, (spina bifida). It can cause skin toxic epidermal necrolysis and Stevens–Johnson syndrome.

In our study we have found based on Glascow outcome scale score effective & good seizure long term control for all the patients treated by Levetiracetam in comparing to those treated by phenytoin & carbamazepine. Jones KE et al, found that Patients on levetiracetam had better long-term outcomes than those on phenytoin. No differences in mortality or side effects between groups except for worsened neurological status and gastrointestinal problems in Levetiracetam-treated patients. Jones KE et al also found higher incidence of abnormal EEG findings in patients levetiracetam group.(14) In our study, it has been found that there were increased incidence of headache, behavioral changes & thrombocytopenia in 5 patients treated by leviteracetam, in comparism to phenytoin & carbamazepine while the incidence of cardiovascular tocxicity with arrhythmia and megaloblastic anaemia due to folate defeciency and hepatotocicity is higher in phenytoin group, (11 of 20 patients). Skin rash and SIADH with hyponatraemia is more in carbamazepine group (9 of 20 patients). A prospective, observational study showed no advantage of levetiracetam over phenytoin, with no difference in seizure rate, adverse drug reactions, or mortality in between the two groups.(4) There were no differences between phenytoin & levetiracetam treated patients in the occurrence of fever, increased intracranial pressure, stroke, hypotension, arrhythmia, thrombocytopenia, liver abnormalities, renal abnormalities, or early death, there was lower incidence of anemia in patients treated with phenytoin.(4,15) Phenytoin increases the threshold of ventricular fibrillation and lower blood pressure as a result of peripheral vasodilatation. (16,17,18) Propylene glycol in phenytoin preparations increase the water solubility cause bradycardia and asystole. (19,20) In our study, it has been found that there were no difference in cost regarding brand company between the three antiepileptic drugs. Pieracci FM, et al found that levetiracetam has advantage over phenytoin without the need of serum level monitoring. (15) Kazerooni et al. calculated the incremental cost-effectiveness ratio of levetiracetam versus phenytoin for each successful seizure prophylaxis regimen to be 360.80 USD. (21) Some studies revealed the superiority of phenytoin over levetiracetam from both the institutional respectively, & patient

perspectives. Recent studies on levetiracetam (LEV) demonstrated that it has neuroprotective effects.(22,23,24) We agree with the study of Meshkini A et al who found that Leviteracetam group experienced fewer complications than Phenytoin (PHT) group. In Meshkini A et al meta-analysis study, they found no superiority of the either drug was seen; however, complications with LEV was less.(25) Similarly, there was slightly lower rate of seizures in the severe TBI group.(26) A gastrointestinal upset & neurologic status dysfunction is associated with phenytoin use. Gregg Vk, found that levetiracetam group showed an improvement in GCS scores. Another study showed that levetiracetam is associated with increased frequency of abnormal EEG findings.(14,27) A systematic review and meta-analysis did find a higher incidence of adverse effects on phenytoin compared to Keppra.(28,29) Phenytoin is highly protein bound medication & in hypoalbuminaemia the ratio of unbound to bound forms becomes less predactable, and toxicity may be seen with low serum level.

So drug serum level is not reliable parameter to reflect the therapeutic index. Jones et al. suggested that Keppra as an alternative to phenytoin with fewer drug-drug interactions & no need for serum monitoring. Levetiracetam is a non–enzyme-inducing anticonvulsant and does not require serum level monitoring and has no significant cutaneous hypersensitivity reactions. (12, 14) On the other hand Phenytoin has serious adverse events including hypersensitivity syndrome, Stevens-Johnson syndrome, purple glove syndrome, and induction of the hepatic cytochrome P450 system. (30,31)

Conclusion

Levetiracetam is a non–enzyme-inducing anticonvulsant that does not require serum level monitoring. This provides a clinical advantage over other antiepileptic drugs. Adverse effects is mild with dizziness, weakness & rarely behavioral changes. It is effective antiepileptic drug to control post traumatic epilepsy, it has advantage over phenytoin & Carbamazepine antiepileptic medications due to fewer side effects & no need of serum level monitoring. Phenytoin is potent & effective antiepileptic drug to control seizures clinically & electrophysiologically (EEG) in acute early stage.

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