

## Fosphenytoin vs Keppra for Status Epilepticus

### Introduction

1. Status epilepticus is a neurological emergency that required urgent assessment and treatment with pharmacologic agents
2. Lorazepam and diazepam are short-acting drugs that can produce immediate effects.
3. Treatment with another long-acting anticonvulsant drug is necessary to prevent recurrent convulsions.
4. Use of IV phenytoin (PHT) in the treatment of status epilepticus dates back to the 50s with fosphenytoin (FPHT) being the primary agent in some institutions.
5. However, both PHT and FPHT can induce adverse reactions such as a reduction in blood pressure, arrhythmia, and allergic symptoms.

<b>Pharmacology</b>		
<b>Properties</b>	<b>Phenytoin/ Fosphenytoin</b>	<b>Levetiracetam (Keppra)</b>
<b>Dose</b>	20 mg/kg/PE (max 1500 mg)	1-4.5 g IV (40-60 mg/kg)*
<b>Administration</b>	<b>Max IV fusion</b> PHT 50 mg/min FPHT 150 mg/min	<b>1g IV Push ~2 min**</b> 1.5-2g IV over 7 min** (2-5 mg/kg/min)
<b>Formulation</b>	IV/PO	IV/PO
<b>PK/PD</b>	Onset: ~30 min*** Half Life: 12-28 hr Excreted: >90% in urine	Onset: 30-45 min Half-life: 6-8 hr Excreted: 66% renal
<b>Adverse Effect</b>	Phlebitis, hypotension, bradycardia & dysrhythmias	Abnormal behavior Dizziness Irritability
<b>Drug Interactions and warnings</b>	Major CYP3A4 Inducer (↓ drug levels)	-----

<b>Compatibility</b>	PHT – only D5W FPHT- D5W or NS	D5W or NS
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\*GHS has utilized this administration based on clinical experience

\*\*PE= Phenytoin equivalents

\*\* Fosphenytoin takes 15 mins to be metabolized to active metabolite in addition to the infusion time

## Overview of Evidence

Author, Year	Design/ sample size	Dosing regimen	Outcome
<b>ESETT</b>	RCT N= >	VPA 30 mg/kg (max 3000 mg) vs LEV 60 mg/kg (max 4500mg) vs PHT 20 mg/kg (max 1500 mg)	Result expected 2020
<b>Nakamura, 2017</b>	*Respective analysis/ n=63	LEV 1000 mg vs FPHT 22.5 mg/kg	<b>No difference</b> in control of seizure(81 vs 85.1%, p=0.69), adverse effects, or transition to PO antiepileptic drug
<b>Gujjar et al, 2017</b>	*Prospective, open-label trial/ n=52	LEV 30 mg/kg vs PHT 20 mg/kg	LEV displayed <b>no statistically significant difference</b> than PHT in SE  Sequential use of these 92–97% of cases controlled without anesthetic agents.
<b>Chakravarthi, 2017</b>	*RCT n=44	LEV <b>20 mg/kg</b> vs PHT 20 mg/kg	Both LEV and PHT were <b>equally effective</b> at termination of seizure activity within 30min and recurrence of seizures within 24 hours
<b>Mundlamuri, 2015</b>	RCT/ n=150	VPA <b>30 mg/kg</b> vs LEV <b>25 mg/kg</b> vs PHT 20 mg/kg	<b>No statistically significant difference</b> in control of SE between VPA (68%), PHT (68 %) and LEV (78%).
<b>Alvarez et al, 2011</b>	Retrospective analysis/ n=466	VPA <b>20 mg/kg</b> LEV <b>20 mg/kg</b> PHT 20 mg/kg	VPA controlled SE in 74.6%, PHT in 58.6%, and LEV in 51.7% of episodes  LEV <b>failed more often than VPA</b> [odds ratio (OR) 2.69

\* Did not reach power according to sample size analysis or did not mention in methods

## **References**

1. Phenytoin. Micromedex [Electronic version]. Greenwood Village, CO: Truven Health Analytics. Retrieved November 12, 2018, from <http://www.micromedexsolutions.com/>
2. Levetiracetam. Micromedex [Electronic version]. Greenwood Village, CO: Truven Health Analytics. Retrieved November 12, 2018, from <http://www.micromedexsolutions.com/>
3. Alvarez V. Second-line status epilepticus treatment: comparison of phenytoin, valproate, and levetiracetam. *Epilepsia*. 2011 Jul;52(7):1292-6.
4. Chakravarthi S. Levetiracetam versus phenytoin in management of status epilepticus. *J Clin Neurosci*. 2015 Jun;22(6):959-63.
5. Mundlamuri RC. Management of generalised convulsive status epilepticus (SE): A prospective randomised controlled study of combined treatment with intravenous lorazepam with either phenytoin, sodium valproate or levetiracetam--Pilot study. *Epilepsy Res*. 2015 Aug;114:52-8.
6. Gujjar AR. Intravenous levetiracetam vs phenytoin for status epilepticus and cluster seizures: A prospective, randomized study. *Seizure*. 2017 Jul;49:8-12.
7. Nakamura K. Efficacy of levetiracetam versus fosphenytoin for the recurrence of seizures after status epilepticus. *Medicine (Baltimore)*. 2017 Jun;96(25):e7206
8. Bleck T. The established status epilepticus trial 2013. *Epilepsia*. 2013 Sep;54 Suppl 6:89-92.