

Intravenous Levetiracetam versus Phenytoin in the Management of Status Epilepticus in Adults: A Systematic Review of Randomised-Controlled Trials

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Abstract

Background: Status epilepticus (SE) represents a neurological emergency with high morbidity and mortality if not promptly treated. Intravenous phenytoin has traditionally been used as second-line anti-epileptic drug (AED) treatment, following benzodiazepines in SE, but is limited by adverse effects that include infusion-site reactions, hypotension and cardiac arrhythmias. Furthermore, as a potent enzyme-inducer, phenytoin may affect the efficacy of other drugs, thereby complicating treatment. Levetiracetam represents a more attractive second-line AED treatment as its administration is relatively straightforward (not requiring cardiac-monitoring) with a more favourable side-effect profile and has minimal drug interactions.

Aim: The purpose of this article is to systematically review the evidence-base comparing the efficacy of intravenous levetiracetam versus phenytoin as second-line AED treatment (following benzodiazepine administration) in the management of SE in adults.

Methods: A literature search was performed in PubMed, EMBASE and Medline, for the search terms: Levetiracetam, phenytoin and Status Epilepticus. Articles were included for review providing they met all of the following inclusion criteria: Original research, published in the English language (up until August 2018) and Randomised-controlled trials (RCTs) of adult patients.

Results: Only 3 studies met the final inclusion criteria. These encompassed a total of 196 patients, from 3 RCTs, of whom 94 were treated with levetiracetam and 102 were treated with phenytoin. All 3 trials suggested equivalent efficacies of phenytoin and levetiracetam in the termination of seizure activity within 24 hours of drug infusions and similar functional outcomes at hospital discharge.

Conclusion: There is a surprising lack of controlled clinical data comparing the efficacy of levetiracetam with phenytoin in the management of SE in adults. Furthermore, existing trials are underpowered due to their small sample sizes, which makes their interpretation limited. Until further robustly designed, well powered, RCTs comparing levetiracetam with phenytoin suggest otherwise, levetiracetam may represent an attractive alternative to phenytoin in second-line AED treatment in SE in adults.

Keywords: Status epilepticus; Levetiracetam; Phenytoin; Anti-epileptic drugs

Introduction

Status epilepticus (SE) is characterized by prolonged seizure activity, or recurrent episodes with no intervening recovery, which persists as a result of failure of mechanisms that would normally terminate a seizure [1]. It arises as a consequence of hyper-synchronous activity of neural ensembles, which is perpetuated by neural plasticity at the molecular, synaptic and network levels [1-3]. As a seizure continues, inhibitory GABAergic-mediated synaptic currents decrease and excitatory NMDA-mediated synaptic activity increases [4]. These changes drive a positive excitatory feedback loop and make it increasingly difficult to terminate a seizure, the longer it persists. Thus, SE must be treated aggressively, typically from 5 minutes after onset, in order to minimize the risk of long-term neurological injury, which is believed to occur after 30 minutes in convulsive SE.

After benzodiazepines, the anti-epileptic drug (AED) of choice has conventionally been intravenous phenytoin [5]. However, this has several limitations, namely infusion-site reactions (e.g. purple glove syndrome), arrhythmia and hypotension, which require close monitoring of cardiac and hemodynamic parameters during

administration, and owing to hepatic enzyme induction, it enhances the metabolism of many drugs. Furthermore, phenytoin can exacerbate certain seizures including myoclonus and absence seizures. These drawbacks are significant and call for an alternative AED to be used as a second-line agent (i.e. after benzodiazepines).

Levetiracetam was the first synaptic vesicle protein 2A (SV2A) ligand used in epilepsy, FDA approved in 2006, and has a broad-spectrum of anti-epileptic activity. It has a favourable side-effect profile, is easy to administer (not requiring cardiac or blood pressure monitoring) and has minimal drug interactions. Thus, levetiracetam may be preferable to phenytoin in benzodiazepine-refractory SE [6].

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Study	N	Patients	Primary outcome measures	Secondary outcome measures	Results	Dosage
Gujjar et al. [8]	52 (LEV 22, PHT 30)	LEV (M:F: 13:9, mean age 38 +/- 19)	Control of seizures with no recurrence over 24 h	- Outcome at hospital discharge - Drug-related adverse effects	Primary: LEV effective in 18/22 (81.8%) vs. PHT effective in 22/30 (73.3%)	IV LEV 30 mg/kg (30 min)
		PHT (M:F: 21:9, mean age 37 +/- 19)			Secondary: Outcome, LEV: Poor MRS 4-6: 45% Outcome, PHT: Poor MRS 4-6: 60% Adverse effects: LEV 2/22, PHT 2/30	IV PHT 20 mg/kg (30 min)
Mundlamuri et al. [9]	100 (LEV 50, PHT 50)	LEV (M:F: 32:18, mean age 34.78 +/- 13.64),	Control of SE: no recurrence of seizures after 30 min of completion of AED infusion with significant clinical improvement over next 24 h or EEG excluded NCSE	- Outcome at hospital discharge (and at 1-month follow-up) - Drug-related adverse effects (-Mortality)	Primary: LEV effective in 39/50 (78%) vs. PHT effective in 34/50 (68%)	IV LEV 25 mg/kg (15 min)
		PHT (M:F: 28:22, mean age 33.24 +/- 13.39)			Secondary: Outcome, LEV: Poor MRS 4-6: 14% Outcome, PHT: Poor MRS 4-6: 26% Adverse effects: LEV 3/50, PHT 3/50	IV PHT 20 mg/kg (50 mg/min)
Chakravarthi et al. [7]	44 (LEV 22, PHT 22)	LEV (M:F: 12:10, mean age 39 +/- 18.4 years)	Successful termination of seizure activity within 30 min of drug infusion	-Recurrence of seizures within 24 h - Outcome at discharge - Drug-related adverse effects (-Need for ventilator) (-Mortality)	Primary: LEV effective in 13/22 (59.1%) vs. PHT effective in 15/22 (68.2%)	IV LEV 20 mg/kg (100 mg/min)
		PHT (M:F: 15:7, mean age 31.82 +/- 12.68 years)			Secondary: Seizure recurrence: LEV 13/22 (59.1%) vs. PHT 16/22 (72.7%) Outcome, LEV: Poor FIM: 13.6% Outcome, PHT: Poor FIM: 18.2% Adverse effects: LEV 0/22, PHT 2/22	IV PHT 20 mg/kg (50 mg/min)

Table 1: A comparison of levetiracetam (LEV) and phenytoin (PHT) in SE in adults. There were no statistical differences in primary or secondary outcome measures. (MRS: Modified Rankin Scale, FIM: Functional Independence Measure).

The purpose of this article is to systematically review the evidence comparing the clinical efficacy of phenytoin with levetiracetam in the treatment of benzodiazepine-refractory SE.

Methods

Randomised-controlled trials (RCTs) comparing intravenous levetiracetam with phenytoin in the treatment of benzodiazepine-refractory SE, in adult patients, were included in this systematic review. A literature search was performed in PubMed, EMBASE and Medline databases in August 2018 for a combination of the search terms: levetiracetam, phenytoin and status epilepticus. For the purposes of this review, SE was defined as seizures persisting for longer than 5 minutes.

The following trial data were extracted: total number (n), number of patients in each study arm (levetiracetam or phenytoin), age, sex, intervention (dose and route of anti-epileptic drug administration), primary outcome measures (termination of SE within a specified time period) and secondary outcome measures (including functional outcomes at hospital discharge and drug-related adverse effects).

Results

Only 3 studies met the inclusion criteria [7-9]. These encompassed a total of 196 patients, from 3 RCTs, of whom 94 were treated with levetiracetam and 102 were treated with phenytoin. All 3 trials suggested equivalent effects of phenytoin and levetiracetam in the management of SE in both primary and secondary outcome measures (Table 1). Except for 2 patients in one study [8] and 3 patients in another [7] (who had

partial or focal SE), the remainder of patients included in the 3 RCTs had generalized convulsive SE.

Discussion

SE carries a high morbidity and mortality if not promptly and aggressively treated [10]. However, it is surprising to note that the evidence underlying the treatment of SE with AEDs, specifically in benzodiazepine-refractory cases, is limited - the evidence is even less in cases of refractory and super-refractory SE [11-13]. In this systematic review, only 3 RCTs were identified that involved a comparison of intravenous phenytoin with levetiracetam as second-line agents in SE (after benzodiazepines). There were no statistically significant differences identified between these 2 AEDs in several primary and secondary outcome measures. For example, both agents showed similar efficacies in the termination of benzodiazepine-refractory SE within 24 hours of administration. There were also no differences in drug-related adverse effects or in functional outcomes at hospital discharge between the two AEDs. Although there were no significant differences in the above outcome measures, the limited data and 'n' numbers make it difficult to draw definitive conclusions as to which AED is more effective in treating benzodiazepine-refractory SE. Given the advantageous characteristics of levetiracetam, including its ease of administration, its broad-spectrum anti-epileptic action, relatively predictable pharmacokinetics, combined with its better safety profile as long-term maintenance AED therapy over phenytoin, levetiracetam is perhaps the preferable option. However, further research is required for confirmation of the comparative clinical efficacy of intravenous levetiracetam with phenytoin in the management of SE in adults.

Conclusion

Although this systematic review has demonstrated clinical equipoise between intravenous phenytoin and levetiracetam in the treatment of benzodiazepine-refractory SE, the evidence underpinning this remains severely limited. Each of the 3 RCTs identified in this review recruited small sample sizes and were therefore significantly underpowered. Further robust, multi-center RCTs, recruiting higher patient numbers, are required for clarification of the preferred AED of choice in the management of benzodiazepine-refractory SE.

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