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Is it a Tie at This Point in the Game? Efficacy of Levetiracetam and Phenytoin for the Second-Line Treatment of Convulsive Status Epilepticus

Levetiracetam Versus Phenytoin for Second-Line Treatment of Pediatric Convulsive Status Epilepticus (EcLiPSE): A Multicentre, Open-Label, Randomized Trial

Lyttle MD, Rainford NEA, Gamble C, Messahel S, Humphreys A, Woolfall K, Roper L, Nablet J, Lee ED, Potter S, Tate P, Iyer A, Evans V, Appleton RE. *Lancet.* 2019;393:2125-34. doi:10.1016/S0140-6736(19)30724-X.

Background: Phenytoin is the recommended second-line intravenous anticonvulsant for treatment of paediatric convulsive status epilepticus in the United Kingdom; however, some evidence suggests that levetiracetam could be an effective and safer alternative. This trial compared the efficacy and safety of phenytoin and levetiracetam for second-line management of pediatric convulsive status epilepticus. Methods: This open-label, randomized clinical trial was undertaken at 30 United Kingdom emergency departments at secondary and tertiary care centers. Participants aged 6 months to less than 18 years, with convulsive status epilepticus requiring second-line treatment, were randomly assigned (1:1) using a computer-generated randomization schedule to receive levetiracetam (40 mg/kg over 5 minutes) or phenytoin (20 mg/kg over at least 20 minutes), stratified by centre. The primary outcome was time from randomization to cessation of convulsive status epilepticus, analyzed in the modified intention-to-treat population (excluding those who did not require second-line treatment after randomization and those who did not provide consent). This trial is registered with ISRCTN, number ISRCTN22567894. Findings: Between July 17, 2015, and April 7, 2018, 1432 patients were assessed for eligibility. After exclusion of ineligible patients, 404 patients were randomly assigned. After exclusion of those who did not require second-line treatment and those who did not consent, 286 randomized participants were treated and had available data: 152 allocated to levetiracetam and 134 to phenytoin. Convulsive status epilepticus was terminated in 106 (70%) children in the levetiracetam group and in 86 (64%) in the phenytoin group. Median time from randomization to cessation of convulsive status epilepticus was 35 minutes (interquartile range: 20 to not assessable) in the levetiracetam group and 45 minutes (24 to not assessable) in the phenytoin group (hazard ratio: 1.20, 95% confidence interval: 0·91-1.60; $P = .20$). One participant who received levetiracetam followed by phenytoin died as a result of catastrophic cerebral edema unrelated to either treatment. One participant who received phenytoin had serious adverse reactions related to study treatment (hypotension considered to be immediately life-threatening [a serious adverse reaction] and increased focal seizures and decreased consciousness considered to be medically significant [a suspected unexpected serious adverse reaction]). Interpretation: Although levetiracetam was not significantly superior to phenytoin, the results, together with previously reported safety profiles and comparative ease of administration of levetiracetam, suggest it could be an appropriate alternative to phenytoin as the first-choice, second-line anticonvulsant in the treatment of pediatric convulsive status epilepticus.

Levetiracetam Versus Phenytoin for Second-Line Treatment of Convulsive Status Epilepticus in Children (ConSEPT): An Open-Label, Multicentre, Randomized Controlled Trial

Dalziel SR, Borland ML, Furyk J, Bonisch M, Neutze J, Donath S, Francis KL, Sharpe C, Harvey AS, Davidson A, Craig S, Phillips N, George S, Rao A, Cheng N, Zhang M, Kochar A, Brabyn C, Oakley E, Babl FE. *Lancet.* 2019;393:2135-45. doi:10.1016/S0140-6736(19)30722-6.

Background: Phenytoin is the current standard of care for second-line treatment of pediatric convulsive status epilepticus after failure of first-line benzodiazepines, but is only effective in 60% of cases and is associated with considerable adverse effects. A newer anticonvulsant, levetiracetam, can be given more quickly, is potentially more efficacious and has a more tolerable adverse effect profile. We aimed to determine whether phenytoin or levetiracetam is the superior second-line treatment for

pediatric convulsive status epilepticus. Methods: ConSEPT was an open-label, multicenter, randomized controlled trial conducted in 13 emergency departments in Australia and New Zealand. Children aged between 3 months and 16 years, with convulsive status epilepticus who failed first-line benzodiazepine treatment, were randomly assigned (1:1) using a computer-generated permuted block (block sizes: 2 and 4) randomization sequence, stratified by site and age ($\leq$5 years, >5 years), to receive 20 mg/kg phenytoin (intravenous or intraosseous infusion over 20 minutes) or 40 mg/kg levetiracetam (intravenous or intraosseous infusion over 5 minutes). The primary outcome was clinical cessation of seizure activity 5 minutes after the completion of infusion of the study drug. Analysis was by intention to treat. This trial is registered with the Australian and New Zealand Clinical Trials Registry, number ACTRN12615000129583. Findings: Between March 19, 2015, and Nov 29, 2017, 639 children presented to participating emergency departments with convulsive status epilepticus; 127 were missed and 278 did not meet eligibility criteria. The parents of one child declined to give consent, leaving 233 children (114 assigned to phenytoin and 119 assigned to levetiracetam) in the intention-to-treat population. Clinical cessation of seizure activity 5 minutes after completion of infusion of study drug occurred in 68 (60%) patients in the phenytoin group and 60 (50%) patients in the levetiracetam group (risk difference: −9.2% [95% confidence interval: −21.9 to 3.5]; $P = .16$). One participant in the phenytoin group died at 27 days because of hemorrhagic encephalitis; this death was not thought to be due to the study drug. There were no other serious adverse events. Interpretation: Levetiracetam is not superior to phenytoin for second-line management of pediatric convulsive status epilepticus.

Commentary

Convulsive status epilepticus (CSE) is a medical emergency which is now formally defined as a tonic–clonic convulsion lasting >5 minutes.[1] Older consensus-based guidelines on the initial treatment of SE[2] have been replaced with modern evidence-based guidelines.[3-5] The medications recommended in the American Epilepsy Society (AES) guideline[3] for the initial treatment of CSE are to first give a bolus of intravenous (IV) lorazepam or diazepam, or IV or intramuscular midazolam, and second to administer a bolus of IV phenytoin/fosphenytoin (PHT) 20 mg PE/kg (maximum, 1500 mg), valproic acid (VPA) 40 mg/kg (maximum, 3000 mg), or levetiracetam (LEV) 60 mg/kg (maximum, 4500 mg).

The AES guideline on the treatment of CSE[3] reviewed the published literature through April 2015. It indicated that in adults, "there is no difference in efficacy between IV lorazepam followed by IV PHT, IV diazepam plus PHT followed by IV lorazepam, and IV phenobarbital followed by IV PHT (level A)." It further indicated that, "insufficient data exist in adults about the efficacy of LEV as either initial or second therapy (level U)", and that, "insufficient data exist in children regarding the efficacy of PHT or LEV as second therapy after failure of a benzodiazepine (level U)."[3] The randomized controlled trial (RCT) supporting the use of LEV for the treatment of CSE was a single open-label class III study in adults and children.[6] With respect to children, this study found that as the first therapy, the success rate of lorazepam (76.3%) was similar to that of LEV 20 mg/kg (75.6%).[6] Given the low level of the evidence behind the recommendations for second-line therapy, the AES guideline recommended that a class I RCT be conducted.[3]

Since April 2015, additional studies have been published on the use of LEV and PHT in the treatment of CSE after an initial benzodiazepine. Mundlamuri et al[7] published a class II RCT comparing LEV 25 mg/kg, PHT 20 mg/kg, and VPA 30 mg/kg in adults with CSE who also received lorazepam. There was no efficacy difference in the subgroups ($P = .44$). Chakravarthi et al[8] published a class II RCT of patients aged 14 to 75 years who first received lorazepam, and secondly received PHT or LEV, both at 20 mg/kg. Phenytoin controlled SE in 68.2% and LEV controlled SE in 59.1% of patients (N.S.). A limitation in the above 3 studies is that the LEV doses selected were probably too low.

Navarro et al[9] conducted a class I superiority RCT comparing 68 adults who received 2.5 gm of LEV to 68 who received placebo after an initial dose of 1 to 2 mg of clonazepam for either CSE or acute repetitive seizures. There was no difference in seizure control 15 minutes after receiving LEV (74%) or placebo (84%). This study[9] indicates that as second-line therapy for CSE, LEV is no more effective than placebo. Finally, Gujjar et al[10] found in a group of 52 patients with mixed focal and CSE, treated initially with lorazepam or diazepam, that the efficacy of LEV 30 mg/kg or PHT 20 mg/kg was similar (82% vs 70%, respectively; $P = .33$).

Anti-seizure drugs (ASDs) can fail to be effective when inadequate doses are used. In pharmacokinetics, a loading dose for an IV drug is defined by the formula: $D_L = V_d \times C_{ss}$ (D_L = loading dose in mg/kg, V_d = volume of distribution, C_{ss} = steady state serum concentration). The V_d of PHT is 0.64 L/kg, LEV is 0.5 to 0.7 L/kg and VPA is 0.22 L/kg. When one is researching the comparative efficacy of different ASDs, appropriate comparable loading doses must be utilized. Therefore, it follows that larger doses of LEV and VPA than used in these past trials should be investigated.

The 2 new RCTs reviewed herein, published in the May 29, 2019 issue of *The Lancet*, were quite similar in design, and indeed used larger loading doses of LEV than older studies. They included children ranging from infancy to adolescence, compared the same 2 ASDs delivered with the same doses over the same duration, and were the first ASD used after failure of an initial benzodiazepine to control CSE. Both studies were conducted in regions where patients were mostly of Caucasian descent.

The EcLiPSE open-label RCT in the United Kingdom was a class II study comparing second-line treatment with loading doses of IV LEV at 40 mg/kg and IV PHT at 20 mg/kg in 286 children. Convulsive status epilepticus was terminated slightly more often and faster with LEV than with PHT ($P = .20$), and serious adverse effects (AEs) occurred with PHT (life-threatening hypotension, worsened focal seizures, and decreased level of consciousness).

The ConSEPT open-label RCT in Australia and New Zealand was also a class II study, and compared second-line treatment with loading doses of IV LEV at 40 mg/kg and IV PHT at 20 mg/kg in 352 children. Clinical cessation of CSE 5 minutes after the completion of the loading dose occurred in 60% of children in the PHT group and 50% in the LEV group ($P = .16$), and there were no serious AEs.

Using the classification of evidence scheme of the American Academy of Neurology,[11] these 2 newest RCTs meet the criteria for class II studies; they are not class I because of their open-label designs. The fact that these 2 studies were consistent in showing that the efficacy of LEV and of PHT is not significantly different allows this conclusion: following administration of a benzodiazepine, IV loading doses of LEV 40 mg/kg and PHT 20 mg PE/kg are probably equally effective in the treatment of children with CSE (Level B).

The Established Status Epilepticus Treatment Trial is a randomized, triple-masked class I trial funded by the United States National Institutes of Health to compare IV fosphenytoin 20 mg PE/kg, VPA 40 mg/kg, and LEV 60 mg/kg in children greater than age 2 years and adults with CSE which does not respond to initial treatment with an adequate dose of a benzodiazepine (NCT01960075). Assignment to a treatment arm is adaptive in order to optimize identification of the most and least effective drug. The doses studied are the same as recommended in the ASD guideline for the treatment of CSE.[3] The Established Status Epilepticus Treatment Trial began in October 2015, is closed to new patients, and has enrolled 478 participants. It is expected to reach completion in October 2019. As a class I study, the results will perhaps provide final evidence of the efficacy and tolerability of these 3 agents at full loading doses in the second-line treatment of both adults and children with CSE.

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