Levetiracetam for posttraumatic epileptic seizure prophylaxis

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In a systematic review and network meta-analysis of randomized controlled trials, no antiepileptic drug had an effect on early or late PTS superior to that of another; however, the sensitivity analysis revealed that phenytoin might prevent early PTS. Additional studies with large sample sizes and a rigorous design are required to obtain high-quality evidence on prophylactic anticonvulsant drug use in patients with traumatic brain injury [1)].

Levetiracetam (LEV) for early PTS prophylaxis is preferred due to its safety and efficacy [2)].

Levetiracetam or phenytoin is often used for seizure prophylaxis in this patient population, but valproic acid may be an appropriate therapeutic alternative in patients with concomitant agitation [3)]

Drug pharmacokinetics (PK) are altered in neurocritically ill patients, and optimal levetiracetam

dosing for epileptic seizure prophylaxis is unknown.

A study evaluates levetiracetam PK in critically ill patients with severe traumatic brain injury (sTBI) receiving intravenous levetiracetam 1000 mg every 8 (LEV8) to 12 (LEV12) hours for posttraumatic epilepsy prophylaxis.

This prospective, open-label study was conducted at a level 1 trauma, academic, quaternary care center. Patients with sTBI receiving seizure prophylaxis with LEV8 or LEV12 were eligible for enrollment. Five sequential, steady-state, postdose serum levetiracetam concentrations were obtained. Non-compartmental analysis (NCA) and compartmental approaches were employed for estimating pharmacokinetic parameters and projecting steady-state trough concentrations. Pharmacokinetic parameters were compared between LEV8 and LEV12 patients. Monte Carlo simulations (MCS) were performed to determine the probability of target trough attainment (PTA) of 6 to 20 mg/L. A secondary analysis evaluated PTA for weight-tiered levetiracetam dosing.

Ten male patients (5 LEV8; 5 LEV12) were included. The NCA-based systemic clearance and elimination half-life were 5.3 ± 1.2 L/h and 4.8 ± 0.64 hours. A one-compartment model provided a higher steady-state trough concentration for the LEV8 group compared with the LEV12 group (13.7 ± 4.3 mg/L vs 6.3 ± 1.7 mg/L; P = 0.008). Monte Carlo simulations predicted regimens of 500 mg every 6 hours, 1000 mg every 8 hours, and 2000 mg every 12 hours achieved therapeutic target attainment. Weight-tiered dosing regimens achieved therapeutic target attainment using a 75 kg breakpoint.

Neurocritically ill patients exhibit rapid levetiracetam clearance resulting in a short elimination half-life. The findings of this study suggest regimens of levetiracetam 500 mg every 6 hours, 1000 mg every 8 hours, or 2000 mg every 12 hours may be required for optimal therapeutic target attainment. A patient weight of 75 kg may serve as a breakpoint for weight-guided dosing to optimize levetiracetam therapeutic target attainment for seizure prophylaxis [4].

Levetiracetam appears to be a safe and effective medication for PTS prophylaxis in combat casualties. The rate of PTSs in combat-related TBI on appropriate prophylaxis is low [5].

A study demonstrated no statistically significant difference in the cumulative incidence of early posttraumatic seizures within 7 days of TBI between three different levetiracetam dosing strategies. After weighing, the ≤ 1000 mg/day levetiracetam group had the lowest rates of early posttraumatic seizures, death without seizure, and in-hospital mortality [6].

AED prophylaxis seems to be effective against early posttraumatic seizures for the pediatric population, with levetiracetam possibly being more effective [7].

Conclusions

Limited Superiority Among AEDs: Systematic reviews and network meta-analysis of randomized controlled trials suggest that no single AED demonstrated a significant superiority over another in preventing early or late PTS following TBI.

Phenytoin for Early PTS Prevention: Sensitivity analysis indicated that phenytoin might be effective in preventing early PTS. However, more high-quality evidence is needed to confirm this finding.

Levetiracetam Preferred for Early PTS Prophylaxis: Levetiracetam (LEV) is preferred for prophylaxis against early PTS due to its safety and efficacy. It has become a commonly used AED in this context.

Valproic Acid as an Alternative: In cases where levetiracetam or phenytoin is not suitable, valproic acid may be considered as an alternative for seizure prophylaxis, particularly in patients with concomitant agitation.

Pharmacokinetic Considerations for Levetiracetam: The pharmacokinetics of levetiracetam can be altered in neurocritically ill patients, including those with severe traumatic brain injury. The optimal dosing regimen for levetiracetam for seizure prophylaxis in this population is not well-established.

Short Elimination Half-Life: Neurocritically ill patients with severe TBI tend to exhibit rapid clearance of levetiracetam, resulting in a short elimination half-life.

Optimal Dosing Regimens: To achieve therapeutic target attainment, dosing regimens of levetiracetam such as 500 mg every 6 hours, 1000 mg every 8 hours, or 2000 mg every 12 hours may be necessary.

Weight-Tiered Dosing: Weight-tiered dosing, with a breakpoint at 75 kg, may be considered to optimize levetiracetam therapeutic target attainment for seizure prophylaxis.

Effectiveness in Combat-Related TBI: Levetiracetam appears to be a safe and effective medication for PTS prophylaxis in combat casualties with traumatic brain injury, resulting in a low rate of posttraumatic seizures when appropriately administered.

Pediatric Population: AED prophylaxis, particularly levetiracetam, seems effective against early posttraumatic seizures in the pediatric population.

In summary, while no AED has demonstrated clear superiority in preventing PTS following traumatic brain injury, levetiracetam is commonly preferred due to its safety and efficacy. Valproic acid may serve as an alternative, and individualized dosing regimens based on pharmacokinetic considerations may be necessary for optimal seizure prophylaxis. Further research with large sample sizes and rigorous designs is needed to establish high-quality evidence in this field.

Test and Answers

What did a systematic review and network meta-analysis of randomized controlled trials reveal regarding antiepileptic drugs (AEDs) for posttraumatic seizure (PTS) prevention in traumatic brain injury (TBI) patients? a) Phenytoin is significantly superior to other AEDs. b) Levetiracetam is the least effective AED. c) No AED had a superior effect on early or late PTS compared to others. d) AEDs are not effective in preventing PTS in TBI patients.

Which AED is preferred for early PTS prophylaxis in TBI patients due to its safety and efficacy? a) Phenytoin b) Valproic acid c) Levetiracetam (LEV) d) Carbamazepine

In patients with concomitant agitation, what AED may be considered as an alternative for seizure prophylaxis? a) Phenytoin b) Levetiracetam c) Valproic acid d) Gabapentin

Why is it important to consider pharmacokinetics in determining the optimal dosing of levetiracetam for seizure prophylaxis in neurocritically ill patients with severe traumatic brain injury (sTBI)? a) Neurocritically ill patients require lower doses of levetiracetam. b) Pharmacokinetics do not vary in this patient population. c) Optimal dosing is well-established, so no adjustments are needed. d) Drug pharmacokinetics are altered in these patients.

What did the study evaluating levetiracetam pharmacokinetics in patients with severe TBI suggest regarding dosing regimens for optimal therapeutic target attainment? a) Higher doses of levetiracetam are not needed. b) Weight-tiered dosing is not effective. c) Regimens of 500 mg every 6 hours or 1000 mg every 8 hours are sufficient. d) Dosing regimens of 500 mg every 6 hours, 1000 mg every 8 hours, or 2000 mg every 12 hours may be required.

What is the primary conclusion regarding levetiracetam as a prophylactic medication for PTS in combat casualties with TBI? a) Levetiracetam is ineffective for combat-related TBI. b) Levetiracetam has a high rate of adverse effects in combat casualties. c) Levetiracetam is safe and effective, resulting in a low rate of PTS. d) Combat casualties with TBI do not require prophylactic AEDs.

In a study comparing different levetiracetam dosing strategies, what group had the lowest rates of early posttraumatic seizures, death without seizure, and in-hospital mortality? a) ≤ 500 mg/day levetiracetam group b) ≤ 750 mg/day levetiracetam group c) ≤ 1000 mg/day levetiracetam group d) ≤ 2000 mg/day levetiracetam group

Which AED appears to be more effective for early posttraumatic seizure prophylaxis in the pediatric population? a) Phenytoin b) Valproic acid c) Levetiracetam d) Carbamazepine

Answers:

c) No AED had a superior effect on early or late PTS compared to others. c) Levetiracetam (LEV) c) Valproic acid d) Drug pharmacokinetics are altered in these patients. d) Dosing regimens of 500 mg every 6 hours, 1000 mg every 8 hours, or 2000 mg every 12 hours may be required. c) Levetiracetam is safe and effective, resulting in a low rate of PTS. c) ≤ 1000 mg/day levetiracetam group c) Levetiracetam

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