Therapeutic Reviews

Series Co-Editors: Andrew Wilcock, DM, FRCP, and Paul Howard BMedSci, MRCP

Therapeutic Reviews aim to provide essential independent information for health professionals about drugs used in palliative and hospice care. Additional content is available on www.palliativedrugs.com. The series editors welcome feedback on the articles (hq@palliativedrugs.com).

Levetiracetam AHFS 28:12.92

Paul Howard, BMedSci, MRCP, Jan Remi, MD, Constanze Remi, MSc, Sarah Charlesworth, BPharm (Hons) DipClinPharm, MRPharmS, Helen Whalley, MSc, FRCP, Rebecca Bhatia, MRCP, Morwenna Hitchens, MRCP, Mary Mihalyo, BS, PharmD, RPh, and Andrew Wilcock, DM, FRCP

Mountbatten Hospice (P.H.), Isle of Wight, United Kingdom; University Hospital of Munich, Germany (J.R. and C.R.), Nottingham University Hospitals (S.C.), Nottingham, United Kingdom; The Royal Bournemouth and Christchurch Hospitals NHS Foundation Trust (H.W.), United Kingdom; Dorothy House Hospice Care (R.B.), Wiltshire, United Kingdom; Prospect Hospice (M.H.), Swindon, United Kingdom; Mylan School of Pharmacy (M.M.), Duquesne University, Pittsburgh, Pennsylvania, USA and University of Nottingham (A.W.), Nottingham, United Kingdom. J Pain Symptom Manage 2018;56:645–649.

Class: Anti-epileptic (SV2A ligand).

Indications: Adjunctive therapy of focal or generalized myoclonic and tonic-clonic seizures; †monotherapy of focal seizures (Authorized in UK); †status epilepticus.

Pharmacology

Levetiracetam binds to synaptic vesicle protein SV2A, interfering with the release of the neurotransmitter stored within the vesicle. It gains access after neurotransmitter release as the vesicles are recycled. Thus, it selectively accumulates in, and inhibits, rapidly firing neurons.[1] Levetiracetam also inhibits potassium and N-type calcium channels.[1,2]

Levetiracetam is a commonly used first-line choice for seizures in palliative care. Such seizures are generally caused by focal brain lesions and are, thus, focal onset, even if this is obscured by rapid secondary generalization. Efficacy and tolerability compare favorably to other anti-epileptic drugs used in focal seizures, both non-cancer and cancer-related.[3-9] It has few drug interactions, can be given IV or SC, and can be used when other anti-epileptics are contra-indicated because of hepatic or cardiac co-morbidities.[10] PR use is also reported; suppositories compounded from levetiracetam tablets produced therapeutic plasma levels.[11]

Anti-epileptics should not be used *prophylactically* in the absence of a history of seizures; in RCTs, they do not reduce the risk.[12] Peri-neurosurgical use is a possible exception, but results are conflicting.[13,14] If used for this indication, prophylactic levetiracetam appears more effective than phenytoin (incidence of seizures 0% vs. 16%).[15]

Although unauthorized, levetiracetam is also used for status epilepticus refractory to benzodiazepines, generally in a dose of 20–30mg/kg given as a single IV bolus. Efficacy appears comparable to fosphenytoin, phenytoin and valproate.[16-19] Trials may have been underpowered to detect clinically significant differences.[19]

Address correspondence to: Dr Andrew Wilcock, DM, FRCP, Hayward House Macmillan Specialist Palliative Care Unit, Nottingham University Hospitals NHS Trust, Nottingham, United Kingdom, NG5 1PB. E-mail: andrew.wilcock@nottingham.ac.uk

Accepted for publication: July 13, 2018.

0885-3924/$ - see front matter
https://doi.org/10.1016/j.jpainsymman.2018.07.012

Levetiracetam is *not* effective for neuropathic pain[20] or social anxiety disorder.[21] Benefit for bipolar disorder and hot flushes is reported,[4,22,23] but has not been confirmed in an RCT.

Food affects the rate but not the extent of its PO absorption. It does not bind to plasma proteins. It readily crosses the blood-brain barrier and its CSF halflife is 3 times longer than that for plasma.[24] A third is metabolized predominantly by non-hepatic hydrolysis; the remainder is excreted by the kidneys unchanged.

Bio-availability ≥95% PO.
Onset of action <3 days PO.
Time to peak plasma concentration 1–2h PO.
Plasma halflife 6–8h.
Duration of action 24h.

Cautions

Renal or severe hepatic impairment (dose adjustment required, see below).

Drug interactions

Clinically significant interactions are unlikely, however caution is advised with concurrent administration of carbamazepine, methotrexate or phenytoin because of isolated reports of toxicity in some patients.[25]

Undesirable effects

Very common (>10%): fatigue, drowsiness, headache.
Common (<10%, >1%): ataxia, hyperkinesis, tremor, dizziness, diplopia, blurred vision, amnesia, abnormal thinking, attention disturbance, behavioural disturbances (emotional lability, irritability, agitation, hostility/aggression, personality disorders), depression, insomnia, anorexia, abdominal pain, diarrhea, dyspepsia, nausea, vomiting, myalgia, rash, pruritus, thrombocytopenia.

Behavioural disturbances occur in 3–4% of patients with epilepsy but only 0.5% of those being treated for other conditions. Risk factors include a history of aggression or psychiatric disturbance.[26,27]

Uncommon (<1%, >0.1%): suicidal ideation (0.2%).
Rare (<0.1%): psychosis, pancreatitis, hepatic failure, acute kidney injury, bone marrow suppression, hyponatremia, extra-pyramidal symptoms, rhabdomyolysis, severe skin reactions.

Dose and use

Anti-epileptics have been associated with suicidal ideation: advise patients to report mood or thought disturbance.

Focal seizures

- start with 250–500mg PO/IV b.i.d.
- if starting with 250mg b.i.d., increase automatically after 2 weeks to 500mg b.i.d. (the minimum effective dose in most people)
- if necessary, increase by 250–500mg b.i.d. every 2 weeks
- maximum dose 1.5g b.i.d.

For IV use, dilute the dose in ≥100mL sodium chloride 0.9% or dextrose 5% and infuse over 15min.

Note. Once daily modified-release PO tablets are available in the USA (see Supply). An oral solution or oral granules (not USA) are available for administration by enteral feeding tubes in some countries; see the PI or SPC for full details.

Status epilepticus refractory to benzodiazepines

Some centres use higher starting doses for status epilepticus refractory to benzodiazepines, e.g.:[16-19]

- loading dose of 1–2g IV (or 20–30mg/kg up to a maximum of 3g) diluted in 100mL sodium chloride 0.9% or dextrose 5% and infused over 15–30min
- after 4–8h, start a maintenance dose of 1g PO/IV b.i.d.

Subcutaneous administration

Levetiracetam can be given †SC b.i.d., diluted in 100mL sodium chloride 0.9% and infused over 30min.[28] The dose is the same PO/SC/IV.

Levetiracetam can also be given by †CSCI diluted with either water for injection or sodium chloride 0.9% when necessary.[29-32]

By CSCI, although there are no formal laboratory compatibility data, levetiracetam is reported to be visually compatible in clinical use with diamorphine (not USA), haloperidol, scopolamine *butylbromide* (not USA), levomepromazine (methotrimeprazine; not USA), metamizole (dipyrone; not UK or USA), methadone, metoclopramide, midazolam, morphine sulfate, oxycodone or ranitidine. Generally, sodium chloride 0.9% is used as diluent and local skin reactions occur in about 5% of patients.[30,33-35]

Alternative SC/CSCI anti-epileptics include lacosamide, midazolam, phenobarbital and valproate.[36,37]

Renal impairment

Because levetiracetam is largely excreted unchanged by the kidneys, the dose should be reduced in patients with renal impairment (Table 1).

Table 1
Dose adjustment for levetiracetam in renal impairment[a]

Creatinine clearance (mL/min/1.73m^2)[b]	Usual maintenance dose[c] (mg)
>80	500−1,500 b.i.d.
50−80	500−1,000 b.i.d.
30−49	250−750 b.i.d.
<30	250−500 b.i.d.

[a]for patients weighing <50kg, the UK SPC recommends dosing on a mg/kg basis
[b]based on the Cockroft-Gault formula adjusted for body surface area
[c]for immediate-release PO/IV products; modified-release products permit the total daily dose to be given once daily.

If on peritoneal dialysis or hemodialysis:
- give 750mg PO/IV on the first day of treatment and 500−1,000mg *once daily* thereafter
- consider giving a 250−500mg supplementary dose immediately after each hemodialysis session or timing the daily dose after the dialysis session.

Hepatic impairment

Because metabolism is non-hepatic and the drug is not protein-bound, there is no need to reduce the dose in hepatic impairment, unless there is associated renal impairment (see Table 1).

Stopping levetiracetam

Reduce by a maximum of 500mg b.i.d. every 2−4 weeks to avoid rebound seizures.

Supply

Levetiracetam (non-proprietary)
Tablets 250mg, 500mg, 750mg, 1g, 28 days @ 750mg b.i.d. = $28.
Oral solution (sugar-free) 100mg/mL, 28 days @ 750mg b.i.d. = $30.
Injection (concentrate for dilution and use as an intravenous infusion) 100mg/mL, 5mL vial = $6.

Modified-release once daily products
Tablets m/r 500mg, 750mg, 28 days @ 1.5g once daily =$220.

Abbreviations/key

†	Off-label use	PO	Per os, by mouth
b.i.d.	bis in die, twice per day	PR	Per rectum
CSCI	Continuous subcutaneous infusion	IV	Intravenous
CSF	Cerebrospinal fluid	RCT	Randomized controlled trial
Min	minute(s)	SC	Subcutaneous
PI	Package insert (USA)	SPC	Summary of Product Characteristics (UK)

References

1. Klitgaard H, et al. Brivaracetam: rationale for discovery and preclinical profile of a selective SV2A ligand for epilepsy treatment. Epilepsia 2016;57:538–548.

2. Madeja M, et al. Reduction of voltage-operated potassium currents by levetiracetam: a novel antiepileptic mechanism of action? Neuropharmacology 2003;45:661–671.

3. Nevitt SJ, et al. Antiepileptic drug monotherapy for epilepsy: a network meta-analysis of individual participant data. Cochrane Database of Systematic Reviews 2017;12:CD011412. www.thecochranelibrary.com.

4. Zaccara G, et al. Comparison of the efficacy and tolerability of new antiepileptic drugs: what can we learn from long-term studies? Acta Neurologica Scandinavica 2006;114:157–168.

5. Lim DA, et al. Safety and feasibility of switching from phenytoin to levetiracetam monotherapy for glioma-related seizure control following craniotomy: a randomized phase II pilot study. Journal of Neuro-oncology 2009;93:349–354.

6. Rossetti AO, et al. Levetiracetam and pregabalin for antiepileptic monotherapy in patients with primary brain tumors. A phase II randomized study. Neuro-oncology 2014;16:584–588.

7. Werhahn KJ, et al. A randomized, double-blind comparison of antiepileptic drug treatment in the elderly with new-onset focal epilepsy. Epilepsia 2015;56:450–459.

8. Glauser T, et al. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. Epilepsia 2013;54:551–563.

9. Vossel KA, et al. Epileptic activity in Alzheimer's disease: causes and clinical relevance. Lancet Neurology 2017;16:311–322.

10. Karceski S, et al. Treatment of epilepsy in adults: expert opinion. Epilepsy and Behavior 2005;7(Suppl 1):S1–S64.

11. Remi C. Personal communication 2018.

12. Guerrini R, et al. The medical and surgical treatment of tumoral seizures: current and future perspectives. Epilepsia 2013;54(Suppl 9):84–90.

13. Weston J, et al. Antiepileptic drugs as prophylaxis for post-craniotomy seizures. Cochrane Database of Systematic Reviews 2015;CD007286. www.thecochrangelibrary.com.

14. Dewan MC, et al. The influence of perioperative seizure prophylaxis on seizure rate and hospital quality metrics following glioma resection. Neurosurgery 2017;80:563–570.

15. Fuller KL, et al. Tolerability, safety, and side effects of levetiracetam versus phenytoin in intravenous and total prophylactic regimen among craniotomy patients: a prospective randomized study. Epilepsia 2013;54:45–57.

16. Glauser T, et al. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the guideline committee of the American Epilepsy Society. Epilepsy Currents 2016;16:48–61.

17. Nakamura K, et al. Efficacy of levetiracetam versus fosphenytoin for the recurrence of seizures after status epilepticus. Medicine 2017;96:e7206.

18. Gujjar AR, et al. Intravenous levetiracetam vs phenytoin for status epilepticus and cluster seizures: A prospective, randomized study. Seizure 2017;49:8–12.

19. Brigo F, et al. Direct and indirect comparison meta-analysis of levetiracetam versus phenytoin or valproate for convulsive status epilepticus. Epilepsy and Behavior 2016;64:110–115.

20. Wiffen PJ, et al. Levetiracetam for neuropathic pain in adults. Cochrane Database of Systematic Reviews 2014;7:CD010943. www.thecochranelibrary.com.

21. Stein MB, et al. Levetiracetam in generalized social anxiety disorder: a double-blind, randomized controlled trial. Journal of Clinical Psychiatry 2010;71:627–631.

22. Dunteman ED. Levetiracetam as an adjunctive analgesic in neoplastic plexopathies: case series and commentary. Journal of Pain and Palliative Care Pharmacotherapy 2005;19:35–43.

23. Thompson S, et al. Levetiracetam for the treatment of hot flashes: a phase II study. Supportive Care in Cancer 2008;16:75–82.

24. Patsalos PN. Clinical pharmacokinetics of levetiracetam. Clinical Pharmacokinetics 2004;43:707–724.

25. Baxter K and Preston CL. Stockley's Drug Interactions. London: Pharmaceutical Press www.medicinescomplete.com (accessed December 2017).

26. Dinkelacker V, et al. Aggressive behavior of epilepsy patients in the course of levetiracetam add-on therapy: report of 33 mild to severe cases. Epilepsy Behaviour 2003;4:537–547.

27. Cramer JA, et al. A systematic review of the behavioral effects of levetiracetam in adults with epilepsy, cognitive disorders, or an anxiety disorder during clinical trials. Epilepsy Behaviour 2003;4:124–132.

28. Lopez-Saca JM, et al. Repeated use of subcutaneous levetiracetam in a palliative care patient. Journal of Pain and Symptom Management 2013;45:e7–e8.

29. Sutherland AE, et al. Subcutaneous levetiracetam for the management of seizures at the end of life. BMJ Supportive and Palliative Care 2018;8:129–135.

30. Remi C, et al. Continuous subcutaneous use of levetiracetam: a retrospective review of tolerability and clinical effects. Journal of Pain and Palliative Care Pharmacotherpy 2014;28:371–377.

31. Ryan S, et al. The use of additional antiepileptic drugs with subcutaneous levetiracetam for the management of seizures at the end of life: a case series. Palliative Medicine 2016;30:NP262.

32. Wells GH, et al. Continuous subcutaneous levetiracetam in the management of seizures at the end of life: a case report. Age and Ageing 2016;45:321–322.

33. Murray-Brown FL, Stewart A. Remember Keppra: seizure control with subcutaneous levetiracetam infusion. BMJ Supportive and Palliative Care 2016;6:12–13.

34. Munich University Hospital. Syringe driver compatability database. Palliative medicine department, 2017. Available from www.pall-iv.de.

35. Palliativedrugs.com Ltd. Syringe Driver Survey Database. www.palliativedrugs.com. Accessed May, 2018.

36. Remi C, et al. Subcutaneous use of lacosamide. Journal of Pain Symptom Management 2016;51:e2–e4.

37. O'Connor N, et al. Sodium Valproate as a continuous subcutaneous infusion: a case series. Journal of Pain and Symptom Management 2017;54:e1–e2.