

LEVITATING LEVETIRACETAM'S STATUS FOR STATUS EPILEPTICUS

Intravenous Levetiracetam in the Treatment of Benzodiazepine Refractory Status Epilepticus. Knake S, Gruener J, Hattemer K, Klein KM, Bauer S, Oertel WH, Hamer HM, Rosenow F. *J Neurol Neurosurg Psychiatry* 2008;79(5):588–589. In 2006, levetiracetam was approved as the first of the newer anticonvulsive drugs as an intravenous formulation (ivLEV) for patients with epileptic seizures who are unable to take oral medication. We report our experience with the use of ivLEV for the treatment of 18 episodes of benzodiazepine refractory focal status epilepticus (SE) in 16 patients, including four patients with secondary generalised SE. SE was controlled in all patients by the given combination of drugs; application of further antiepileptic medications after ivLEV was necessary in two episodes. No severe side effects occurred. Our data suggest that ivLEV may be an alternative for the treatment of SE in the future, even in patients that did not respond to benzodiazepines. A large prospective, randomised, controlled study is warranted to investigate the efficacy and safety of ivLEV for the treatment of SE.

COMMENTARY

When the first intravenous (IV) medication (typically a benzodiazepine) does not stop status epilepticus (SE), administration of subsequent agents often is ineffective. In the landmark prospective, randomized clinical trial for the treatment of SE, the second agent was successful in only 7% of patients if the first agent failed (1). Although anesthetic doses of midazolam and propofol are quite effective in this situation, they frequently require respiratory support and long-term critical care. Thus, there is a need for effective IV agents that do not result in prolonged sedation or respiratory compromise. IV valproate has shown significant promise in this regard (2), and now IV levetiracetam is demonstrating similar promise.

In 2006, the United States Food and Drug Administration approved the IV formulation of levetiracetam for instances in which oral medication cannot be used: up to 1,500 mg in a single dose, administered over 15 minutes after dilution (compatible with most or all diluents). IV levetiracetam was not approved for higher doses or for use in status epilepticus. However, studies rapidly appeared showing that up to 2,500 mg over 5 minutes and up to 4,000 mg over 15 minutes could be administered safely to normal volunteers (3).

The current retrospective study by Knake et al. is the first report involving a reasonable number of patients with SE who were treated with IV levetiracetam. All patients had focal-onset SE and failed treatment with a benzodiazepine (usually lorazepam) prior to receiving IV levetiracetam. The mean levetiracetam loading dose was 944 mg, usually given over 30 minutes, followed by a mean maintenance dose of 2,166 mg/day. There were no serious adverse effects, and intubation was avoided in 17/18 episodes. Efficacy was impressive, with clinical seizure activity stopping in all patients and rarely recurring. Five patients had failed IV valproate prior to receiving IV

levetiracetam; only one had failed IV phenytoin first. All patients were discharged on oral levetiracetam, with a mean dose of just over 2,000 mg/day.

The limitations of the study should be kept in mind. The group of patients was highly selective and received IV levetiracetam for SE (rather than IV phenytoin or fosphenytoin) for a particular, clinically relevant reason—most commonly because of hepatic failure or to avoid interactions with anticoagulants or chemotherapy. The study was open label and retrospective; thus, the possibility of publication bias also must be considered. Perhaps hundreds of centers have reviewed their experience with IV levetiracetam, but only those with highly impressive results go on to submit for publication. Indeed, the outcomes seem almost too good to be true. Finally, four of the eight authors have received speakers' honoraria or research grants from the manufacturer of levetiracetam, as has the author of this commentary. Nonetheless, the report by Knake et al. is quite encouraging and provides justification for future prospective clinical trials.

How does levetiracetam stop seizure activity? The mechanism remains somewhat unclear, but its study has led to interesting new insights. Levetiracetam is not effective in some of the classic animal models of acute seizures, such as maximal electroshock and pentylenetetrazol, but it is effective against several models of chronic epilepsy, such as kindling (4). This finding might suggest that it would not be effective in SE, and animal studies have been conflicting in this regard (4). Levetiracetam seems to desynchronize neuronal networks without affecting normal neuronal transmission, thereby preventing burst firing. It may prevent early changes in gene expression during kindling and modulates effects of calcium and GABA. The most interesting discovery has been that levetiracetam binds to synaptic vesicle protein 2A, a regulator of vesicular traffic and therefore, of neurotransmitter release, and the potency of binding seems to correlate with antiseizure efficacy. SV2A knockout mice have growth retardation, progressive seizures, and premature death. Exactly how levetiracetam binding to SV2A leads to decreased seizures is unclear. Some investigators have argued that IV

levetiracetam is neuroprotective or antiepileptogenic, and there is some evidence that this is the case in models of epilepsy, stroke, trauma, and subarachnoid hemorrhage. However, there is also evidence to the contrary, as recently reviewed in this journal (5).

Does levetiracetam need to be given intravenously? The answer to this question is not clear, as oral absorption is typically excellent. However, it has not been studied in critically ill patients or those under sedation. Until the pharmacokinetics in the acute setting is known, it may be preferable to utilize IV administration during acute seizure circumstances. Having promptly available serum level determination may allow for a more rapid, yet safe switch to oral administration. There are several studies that have found oral levetiracetam (via a nasogastric tube) to be effective in acute, refractory seizures, including nonconvulsive SE (6–8).

Shortly after the current study was published, a similar study reported on the use of IV levetiracetam in 50 critically ill patients, including 24 with SE (9). SE ceased in two-thirds of the cases at a mean dose of 1,780 mg, typically given over 15–30 minutes, with seizure cessation confirmed by EEG. Two of the 50 patients given IV levetiracetam developed transient thrombocytopenia (dropping from normal to 55,000 and 82,000); no serious adverse effects were noted.

Is IV levetiracetam ready to be used routinely for the management of SE? The answer to this question is: probably not quite yet, as there have been no comparative, prospective, or randomized trials. In addition to determining its efficacy more definitively, it will be important to follow the incidence of agitation and infections in patients administered levetiracetam (IV or enterally), as both of these adverse effects are consistently more frequent for individuals on levetiracetam than on placebo in clinical trials (10), and critically ill patients are at particularly high risk for these issues. Nonetheless, IV levetiracetam has many attractive features that will ensure its common use in the inpatient setting, including: mostly renal clearance, virtually no interactions, rare allergic reactions, minimal respiratory and cardiovascular effects with IV loading, broad-spectrum efficacy, and ease of use. No other IV medication for seizures

shares these features. The current report provides justification for continued use of IV levetiracetam for critically ill patients with seizures (including SE in carefully selected cases) and for assessing it in future clinical trials on the treatment of SE.

by Lawrence J. Hirsch, MD

References

1. Treiman DM, Meyers PD, Walton NY, Collins JF, Colling C, Rowan AJ, Handforth A, Faught E, Calabrese VP, Uthman BM, Ramsay RE, Mamdani MB. A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. *N Engl J Med* 1998;339(12):792–798.
2. Hirsch LJ. The status of intravenous valproate for status. *Epilepsy Curr* 2007;7(4):96–98.
3. Ramael S, Daoust A, Otoul C, Toublanc N, Troenaru M, Lu ZS, Stockis A. Levetiracetam intravenous infusion: a randomized, placebo-controlled safety and pharmacokinetic study. *Epilepsia* 2006;47(7):1128–1135.
4. De Smedt T, Raedt R, Vonck K, Boon P. Levetiracetam: the profile of a novel anticonvulsant drug—part I: preclinical data. *CNS Drug Rev* 2007;13(1):43–56.
5. Dudek FE, Bertram EH, Staley KJ. Antiepileptogenesis therapy with levetiracetam: data from kindling versus status epilepticus models. *Epilepsy Curr* 2008;8(1):28–30.
6. Falip M, Carreno M, Amaro S, Donaire A, Delgado R, Toledo M, Maestro I. Use of levetiracetam in hospitalized patients. *Epilepsia* 2006;47(12):2186–2188.
7. Rossetti AO, Bromfield EB. Determinants of success in the use of oral levetiracetam in status epilepticus. *Epilepsy Behav* 2006;8(3):651–654.
8. Rupprecht S, Franke K, Fitzek S, Witte OW, Hagemann G. Levetiracetam as a treatment option in non-convulsive status epilepticus. *Epilepsy Res* 2007;73(3):238–244.
9. Ruegg S, Naegelin Y, Hardmeier M, Winkler DT, Marsch S, Fuhr P. Intravenous levetiracetam: treatment experience with the first 50 critically ill patients. *Epilepsy Behav* 2008;12(3):477–480.
10. De Smedt T, Raedt R, Vonck K, Boon P. Levetiracetam: part II, the clinical profile of a novel anticonvulsant drug. *CNS Drug Rev* 2007;13(1):57–78.