Polytherapy as first-line in status epilepticus: should we change our practice? "Time is brain"!

Ashalatha Radhakrishnan

R. Madhavan Nayar Center for Comprehensive Epilepsy Care (RMNC), Department of Neurology, Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST), Trivandrum, Kerala, India

Correspondence to: Dr. Ashalatha Radhakrishnan. Consultant Neurologist & Epileptologist, R. Madhavan Nayar Center for Comprehensive Epilepsy Care (RMNC), Department of Neurology, Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST), Trivandrum 695011, Kerala, India. Email: drashalatha@sctimst.ac.in or ashalatharadhakrishnan@gmail.com.

Provenance: This is a Guest Commentary commissioned by Editor-in-Chief Rafael Rosell, MD, PhD [Cancer Biology and Precision Medicine Program, Catalan Institute of Oncology, Hospital Germans Trias i Pujol, Ctra Canyet, Badalona (Barcelona), Spain].

Comment on: Navarro V, Dagron C, Elie C, *et al*. Prehospital treatment with levetiracetam plus clonazepam or placebo plus clonazepam in status epilepticus (SAMUKeppra): a randomised, double-blind, phase 3 trial. Lancet Neurol 2016;15:47-55.

Submitted Oct 25, 2016. Accepted for publication Oct 29, 2016.

doi: 10.21037/atm.2016.11.37

View this article at: http://dx.doi.org/10.21037/atm.2016.11.37

Status epilepticus (SE) is one of the most common neurologic emergencies, and is associated with significant mortality ranging from 3% to 40% in various studies (1). "Time is brain" is as important in SE as in any vascular neurologic emergencies since early and prompt treatment offers better outcome. Two decades ago in a pivotal study, Lowenstein *et al*. demonstrated that seizures are easier to control if treatment is initiated earlier (2). Current guidelines recommend a step-wise approach using different antiepileptic drugs (AEDs) with benzodiazepines (BZDs) being the first-line treatment. To provide a more effective and rapid treatment at the earliest, there are suggestions using more than one drug as first-line treatment, especially in a pre-hospital setting outside the premise of a hospital (3).

Evidence supports the use of BZP, mostly lorazepam (LZP), diazepam (DZP) and midazolam (MDZ) as initial monotherapy for SE. But there is paucity of data on the use of non-sedating AEDs such as phenytoin (PHT), valproic acid (VPA), levetiracetam (LEV), lacosamide (LCM) etc., without previous BZP administration or in combination with a BZP. Considering the heterogeneity of SE as regards to etiology, age groups affected, the time elapsed and the inadequacy in diagnosing non-convulsive SE, makes a "one fits all" approach irrational.

In this context, Navarro and colleagues in *Lancet Neurology*, 2016 present the results of the SAMUKeppra study, which is a novel and well-designed, randomised, double-blind, placebo-controlled trial (RCT) comparing the efficacy of LEV as an add-on treatment to CLZ for the pre-hospital treatment of generalised convulsive status epilepticus (CSE) (4). The results did not show any difference for the primary outcome i.e., cessation of convulsions at 15 minutes after instituting the drug(s). Also, post-hoc analyses of safety and efficacy endpoints did not differ. Seizures stopped in 74% of 68 patients receiving LEV with CLZ and 84% of 68 patients in the control group who received 1–2 mg of CLZ. These response rates are higher than those reported in previous RCTs of 59% and 65% for intravenous (IV) LZP (4 mg or 0.1 mg/kg) and 73% for intramuscular MDZ (10 mg) (5-7). But Navarro's trial was limited to only a small number of patients; therefore the results should be interpreted with caution. Also, they gave a second dose of CLZ (1 mg more, if the seizures continued despite the initial dosage of 1 mg) before they assessed the primary outcome. The response rate of 57% after the first dose thus increased to 84% after second dose of CLZ.

First, let us examine the option of choosing from the therapeutic armamentarium, a first-line AED in a pre-hospital setting which can be administered with BZP. There are only few retrospective studies, case series and then few meta-analyses addressing this issue which have

concluded that VPA, LEV and LCM are equally good options as AEDs which can be used once BZP fails or even as first-line (8-14).

PHT is the conventional second-line agent in treating CSE, but it is limited by hypotension, lethal arrhythmias, allergies, drug interactions, and extravasation causing major thrombophlebitis making it a less ideal choice to be used with or without BZP as first-line therapy especially in a pre-hospital setting. IV VPA is an effective and safe alternative to PHT. VPA can be administered rapidly through IV route, has broad-spectrum action, and has fewer acute side-effects. LEV and LCM are also well tolerated IV AEDs with fewer interactions, allergies, and contraindications, making them potentially effective drugs (8-14). But the option of choosing them as first-line agents as monotherapy or as polytherapy with BZP is limited by the lack of RCTs.

The next issue to be debated is the position of CLZ as first-line treatment in CSE. The RAMPART study, compared MDZ given through an intramuscular (IM) autoinjector, with IV LZP given by the paramedics prior to arrival to the emergency department, concluding superiority of MDZ (6). MDZ is effective and safe in the pre-hospital setting when administered intramuscularly, buccally, or nasally. Regular use of home rescue medications such as nasal/buccal MDZ by patients and caregivers for prolonged seizures and seizure clusters may prevent SE, prevent emergency room visits, improve quality of life, and lower health care costs. Several studies have compared different BZDs incorporating several routes of administration, with notable heterogeneity in the methodology. A recent meta-analysis of various BZPs used in RCTs for treatment of SE looked into the seizure cessation within 10 minutes of sublingual LZP, buccal MDZ, intrananasal MDZ, rectal DZP, and IV DZP; they concluded that IM and intranasal MDZ resulted in the fastest and most persistent seizure termination. The meta-analysis, however, did not include CLZ (15). MDZ is commonly used in Britain, while LZP in the US and Asian countries and the continental Europeans commonly use CLZ in SE. CLZ has less affinity to the GABA-A receptor than LZP, it is lipophilic with rapid onset of action, with more rapid entry to the brain after IV administration (16). In addition, its long elimination half-life (up to 40 hours) is important for rapid initial treatment of SE, thus reducing the chances of recurrence in the acute setting. CLZ (0.015 mg/kg) can also be administered as a rapid bolus over 30 seconds or less, which is faster than the rate of LZP administration (2 mg/minute). But no Class I evidence exists for CLZ usage, unlike with other BZPs (5-7).

Alvarez *et al*. conducted a prospective observational study at four different centers in Switzerland and Boston (16). IV CLZ was the first-line treatment for SE in Switzerland, and IV LZP in Boston. MDZ remained the alternative treatment in all centers. Of 177 patients, 72 (41%) received CLZ, 82 (46%) received LZP, and 23 (13%) received MDZ as first-line. The etiology, severity of SE and mean time to treatment were comparable across the three groups, which were the highlights of this study. Only 75% of patients received BZP as first-line treatment; among these, 59% received insufficient doses. The loading dose was considered sufficient in the CLZ group than the other two groups. LZP group had longer duration of SE and were significantly more likely to become refractory than the other two groups. Even after adjustment for the loading dose, the risk of refractoriness was higher with LZP than CLZ, with no difference between CLZ and MDZ. In a subgroup analysis of CSE, similar results were obtained with LZP resulting in more refractoriness and higher number of AEDs needed to control SE. Mortality was related to the etiology and severity of SE but was neither different among the three groups nor influenced by second-line treatment. This study emphasizes the issue of underdosing BZDs which causes less than satisfactory results which are falsely labelled as "BZP-refractoriness". Additionally, it suggests that CLZ may be an appropriate first-line AED in SE and may even be superior to LZP, which needs to be explored further. Instead of the recommended 0.15 mg/kg dose of LZP, physicians commonly administer smaller boluses initially and repeat it later if seizures do not abate. One can surmise that it is due to the fear of respiratory compromise, but this can jeopardise the outcome in SE. In this context, the role of CLZ at a dose of 0.015 mg/kg (1 mg bolus dose in adults) becomes a valuable option as it seldom causes respiratory depression. In the aforementioned clinical trial of CLZ, done over 6 to 9 weeks with doses of 3 mg or more, there was no respiratory depression (16). In many of the trials, the route of administration was oral, since CLZ has oral bioavailability of 80–90%. Although class I evidence is lacking to prove that IV CLZ is better in SE, available evidences calls for conducting RCTs to prove or disprove it as a better option in SE as first-line BZP.

The SAMUKeppra study (4) is unique and novel since combination of two drugs i.e., BZP plus any other non-BZP derivative in the pre-hospital setting has not been thoroughly investigated since as emphasised earlier a very aggressive, early treatment envisaging a "BZP-refractory group" would be an ideal regimen remaining

yet unexplored. Such polytherapy trials in the specified time frame are worth pursuing homogeneously world-over after obtaining robust scientific evidence. Addition of LEV to BZP, the choice made by Navarro and colleagues, is a plausible combination given that LEV has been proved to be efficacious at least as second line add-on drug in many studies, although in this under-powered trial, especially where CLZ was used in double dosages than what is recommended, LEV could not prove its merit (17-21). Its ease of administration in 5 minutes and relative lack of side effects especially cardio-respiratory adverse effects makes it a rational drug for combining with BZP. LEV has also been shown to be neuroprotective in animal models (22). The Established Status Epilepticus Treatment Trial (ESETT) on the comparison of LEV with fosphenytoin or VPA for "benzodiazepine-refractory" CSE is in progress (23,24).

Overall, the use of CLZ instead of LZP or MDZ as in SAMUKeppra trial along with one another safe AED is worth pursuing in a pre-hospital setting due to the potential benefits of CLZ and LEV as discussed earlier. Partial status epilepticus was not assessed and pediatric age group were excluded in this trial. The negative results and the authors' recommendation to explore different drugs in future trials make it unlikely that the pharmaceutical sponsoring had much influence on this trial.

Overall, this trial opens many future avenues to be explored in the early treatment of SE.

(I) Which is the best BZP amongst all as first-line drugs?

(II) Are we under-dosing the persons who are seizing with BZP which may be the reason that at least a good majority get labelled as "BZP-refractory" and one move on to second-line therapies?

(III) Can we use CLZ as the first-line BZP considering its ideal pharmacodynamics, longer duration of action and lack of dreaded side effects akin to other BZPs?

(IV) Can LEV or VPA or LAC be tried simultaneously in patients who do not respond to BZP in 5 minutes- is polytherapy a better option?

Acknowledgements

None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

References

1. Koubeissi M, Alshekhlee A. In-hospital mortality of generalized convulsive status epilepticus: a large US sample. Neurology 2007;69:886-93.
2. Lowenstein DH, Alldredge BK. Status epilepticus at an urban public hospital in the 1980s. Neurology 1993;43:483-8.
3. Alvarez V, Rossetti AO. Monotherapy or Polytherapy for First-Line Treatment of SE? J Clin Neurophysiol 2016;33:14-7.
4. Navarro V, Dagron C, Elie C, et al. Prehospital treatment with levetiracetam plus clonazepam or placebo plus clonazepam in status epilepticus (SAMUKeppra): a randomised, double-blind, phase 3 trial. Lancet Neurol 2016;15:47-55.
5. Alldredge BK, Gelb AM, Isaacs SM, et al. A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. N Engl J Med 2001;345:631-7.
6. Silbergleit R, Lowenstein D, Durkalski V, et al. Lessons from the RAMPART study--and which is the best route of administration of benzodiazepines in status epilepticus. Epilepsia 2013;54 Suppl 6:74-7.
7. Treiman DM, Meyers PD, Walton NY, et al. A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. N Engl J Med 1998;339:792-8.
8. Bachhuber A, Lasrich M, Halmer R, et al. Comparison of Antiepileptic Approaches in Treatment of Benzodiazepine Nonresponsive Status Epilepticus. CNS Neurosci Ther 2016;22:178-83.
9. Zheng F, Du C, Wang X. Levetiracetam for the treatment of status epilepticus. Expert Rev Neurother 2015;15:1113-21.
10. Trinka E, Höfler J, Zerbs A, et al. Efficacy and safety of intravenous valproate for status epilepticus: a systematic review. CNS Drugs 2014;28:623-39.
11. Yasiry Z, Shorvon SD. The relative effectiveness of five antiepileptic drugs in treatment of benzodiazepine-resistant convulsive status epilepticus: a meta-analysis of published studies. Seizure 2014;23:167-74.
12. Kellinghaus C, Berning S, Immisch I, et al. Intravenous lacosamide for treatment of status epilepticus. Acta Neurol Scand 2011;123:137-41.
13. Höfler J, Unterberger I, Dobesberger J, et al. Intravenous lacosamide in status epilepticus and seizure clusters. Epilepsia 2011;52:e148-52.

14. Kellinghaus C, Berning S, Stögbauer F. Intravenous lacosamide or phenytoin for treatment of refractory status epilepticus. Acta Neurol Scand 2014;129:294-9.
15. Arya R, Kothari H, Zhang Z, et al. Efficacy of nonvenous medications for acute convulsive seizures: A network meta-analysis. Neurology 2015;85:1859-68.
16. Alvarez V, Lee JW, Drislane FW, et al. Practice variability and efficacy of clonazepam, lorazepam, and midazolam in status epilepticus: A multicenter comparison. Epilepsia 2015;56:1275-85.
17. Klitgaard H, Matagne A, Grimee R, et al. Electrophysiological, neurochemical and regional effects of levetiracetam in the rat pilocarpine model of temporal lobe epilepsy. Seizure 2003;12:92-100.
18. Knake S, Gruener J, Hattemer K, et al. Intravenous levetiracetam in the treatment of benzodiazepine refractory status epilepticus. J Neurol Neurosurg Psychiatry 2008;79:588-9.
19. Rüegg S, Naegelin Y, Hardmeier M, et al. Intravenous levetiracetam: treatment experience with the first 50 critically ill patients. Epilepsy Behav 2008;12:477-80.
20. Alvarez V, Januel JM, Burnand B, et al. Second-line status epilepticus treatment: comparison of phenytoin, valproate, and levetiracetam. Epilepsia 2011;52:1292-6.
21. Misra UK, Kalita J, Maurya PK. Levetiracetam versus lorazepam in status epilepticus: a randomized, open labeled pilot study. J Neurol 2012;259:645-8.
22. Griffin CE 3rd, Kaye AM, Bueno FR, et al. Benzodiazepine pharmacology and central nervous system-mediated effects. Ochsner J 2013;13:214-23.
23. Bleck T, Cock H, Chamberlain J, et al. The established status epilepticus trial 2013. Epilepsia 2013;54 Suppl 6:89-92.
24. Cock HR; ESETT Group. Established status epilepticus treatment trial (ESETT). Epilepsia 2011;52 Suppl 8:50-2.

Cite this article as: Radhakrishnan A. Polytherapy as first-line in status epilepticus: should we change our practice? "Time is brain"! Ann Transl Med 2016;4(24):544. doi: 10.21037/atm.2016.11.37

