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Mono- or polytherapy for first-line treatment of status epilepticus?

Vincent Alvarez, MD[1,2,3] and Andrea O. Rossetti, MD[2]

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"*Status epilepticus diagnosis, management and outcome: an update*"

Affiliations:

[1] Department of Neurology, Hôpital du Valais, Sion, Switzerland

[2] Department of Clinical Neurosciences, CHUV and University of Lausanne, Lausanne, Switzerland

[3] Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, Boston, USA

Contact:

Vincent Alvarez

Service de Neurologie – Etage C

Hôpital du Valais

Av. du Grand-Champsec 80

1950 Sion, Switzerland

Mail: vincent.alvarez@hopitalvs.ch

Phone: +41 27 603 40 00

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Abstract:

Status epilepticus (SE) is one of the most frequent neurological emergencies, and a rapid and effective treatment is warranted. Current guidelines recommend a step-wise approach using a sequence of different anti-epileptic drugs (AED) with be benzodiazepines (BZD) being the first treatment proposed. In order to provide a more effective treatment as soon as possible, some authors have suggested using a combined polytherapy as first line treatment. Strong evidences support the use of BZD, mostly lorazepam and midazolam as initial monotherapy treatment for SE. Insufficient data are available to support the use of non-sedating AED as phenytoin, valproic acid or levetiracetam without a previous BZD administration. Studies assessing the role of a combined initial therapy are rare, if not missing. Moreover, due to the wide range of SE etiologies a "one fits all" initial polytherapy seems difficult to achieve. After reviewing the available evidences, guidelines and current practices regarding mono- and polytherapy as first line treatment in SE in adults, we propose a rational algorithm for early anti-seizure treatment in SE.

1. Introduction:

Status epilepticus (SE) is one of the most frequent neurological emergencies and is associated high mortality ranging from 3-33% (Koubeissi and Alshekhlee, 2007), (Knake et al., 2001), (Vignatelli et al., 2003); therefore, a rapid and effective treatment is recommended (Brophy et al., 2012), (Meierkord et al., 2010). Current American (Brophy et al., 2012) and European (Meierkord et al., 2010) guidelines suggest a step-wise approach using a sequence of different anti-epileptic drugs (AED). The first recommended line of treatment is an intravenous (iv) benzodiazepine (BZD), based on class I evidence (Leppik et al., 1983), (Treiman et al., 1998), (Alldredge et al., 2001), (Silbergleit et al., 2012). In case of ongoing seizures, a second line of AED is proposed. However in order to provide a more rapid and incisive treatment some authors have proposed to use a combined polytherapy as first line, by merging the first and second line (Millikan et al., 2009), (Navarro et al., 2011).

The aim of this article is to review the available data and current practice regarding the early anti-seizure medication in SE and to clarify if there is enough evidence supporting rather a mono- or a combined polytherapy approach for the initial anti-seizure treatment in SE management in adults.

2. Monotherapy for first-line treatment: existing evidence

2.1 Benzodiazepines:

Several randomized-control studies showing the efficacy of BZD as first line therapy have been published. The first one was performed in the early eighties (Leppik et al., 1983); a total of 70 adult patients with all type of SE were randomized between iv lorazepam (LZP) 4 mg or iv diazepam (DZP) 10 mg. LZP controlled the seizures in 89% of cases, and DZP in 76%; this difference didn't reach a statistical significance. The Veteran Affairs (VA) cooperative study (Treiman et al., 1998), performed the following decade, was a double-blind trial conducted in 16 centers in the US, and randomized 384 patients with generalized convulsive

SE into four arms: iv LZP 0.1 mg/kg, iv phenobarbital (PB) 15 mg/kg, iv DZP 0.15 mg/kg associated with iv phenytoin (PHT) 18 mg/kg, or iv PHT 18 mg/kg alone. LZP was the most efficient to stop the seizure with 64.9% of success; this was statistically better than PHT alone. A third study randomized in a pre-hospital setting 205 patients with general convulsive SE between iv LZP 2 mg, iv DZP 5 mg and placebo (Alldredge et al., 2001). Only 21.1% of the SE episodes were controlled by placebo, while DZP and LZP stopped the seizures in 42.6% and 59.1% of cases, respectively; here again there was no statistical difference among the benzodiazepines, while both agents were better than placebo. The RAMPART study is the most recent trial (Silbergleit et al., 2012), where 893 adult and pediatric patients with generalized convulsive SE were randomized to iv LZP 4 mg and intramuscular (im) midazolam (MDZ) 10 mg for emergent pre-hospital treatment, and designed as a non-inferiority trial. There was a trend in favor of im MDZ over iv LZP for early seizure control (73.4% vs. 63.4%); this difference is likely explained by the speed and easiness of administration rather than the drug itself. Indeed, in that trial the im route was clearly faster than the iv one.

Finally, it is also important to mention that iv clonazepam (CLZ) 0.015 mg/kg, which is registered and used in many European and South-American countries to treat SE (Shorvon et al., 2008) has been far less extensively studied than the aforementioned compounds. A trial performed in 61 patients with severe refractory epilepsy and repeated episodes of SE found that the CLZ efficacy was comparable to LZP (Sorel et al., 1981), and an open study reported CLZ to be rapidly effective and safe in SE management with a mean time to seizure control of 1.75 min (Singh and Le Morvan, 1982). More recently a observational study of 177 (Alvarez et al., 2015), showed that CLZ seems to be an effective alternative to LZP and MDZ.

2.2 Non-sedating AED

Non-sedating AEDs have also been studied as first line agent. A trial performed in India, assessed the efficacy of valproic acid (VPA) 30 mg/kg and PHT 18mg/kg as first line treatment by randomizing 68 patients with convulsive SE (Misra et al., 2006). VPA aborted the seizures in two third of patients, while PHT only in 42%, suggesting that VPA may be more effective. This study was however underpowered to draw definitive conclusions. Similar results were found in a prospective open-label assessment of 74 patients suffering from a SE or acute repetitive seizures (Gilad et al., 2008). A rescue medication was needed for 12.3% of patients in the VPA group and 12% in the PHT group. Levetiracetam (LEV) has also been studied in this setting; this has been recently summarized (Shin and Davis, 2013). There is however only one randomized study from India including 79 patients, showing that LEV 20 mg/kg controls convulsive SE in three quarters of patients, a similar rate than LZP 0.1 mg/kg (Misra et al., 2012); slightly more patients were seizure free at 24 hours in the LEV group. Beside this single prospective study, some retrospective surveys with limited numbers of subjects reported favorable outcome for patients treated with LEV as a first line therapy in different population including 9 elderly patients (Fattouch et al., 2010), 2 subjects at high risk of respiratory distress (Berning et al., 2009) and 12 (Rüegg et al., 2008) and 17 critically ill patients (Nau et al., 2009).

2.3 Conclusions

While there are strong evidences to support the use of BZD as first line treatment, favoring among them the compound that may be administered most easily, evidences supporting the use of PHT, VPA or LEV skipping BDZ are far less robust.

3. Polytherapy for first-line treatment: available evidences

3.1 Existing evidence

In general, well-conducted studies beyond the first treatment line are extremely scarce (Rossetti and Lowenstein, 2011), and the knowledge gap regarding a combined polytherapy approach is even bigger. The VA cooperative study (Treiman et al., 1998) included one arm of a combined treatment including DZP 0.15 mg/kg given together with PHT 18 mg/kg. This polytherapy group showed however a (non-significant) lower rate of seizure control than LZP or PB (55.8% vs. 64.9% and 64.2% respectively), while it was better than PHT alone. Of note, the primary outcome was seizure control 20 minutes after the start of drug infusion, and PTH was delivered at a maximal rate of 50mg/min; PHT infusion might therefore not have been completed at the time of the primary outcome assessment. There was no difference between the four groups regarding seizure recurrence rate at 24 hours and clinical outcome at 30 days.

An ongoing study is assessing in France the question of combined early therapy by randomizing patients between CLZ 1mg + LEV 2500 mg iv versus CLZ 1mg + placebo (Navarro et al., 2011). Results have not been published yet, but this attempt may potentially provide very instructive results. Another French observational study focusing on pre-hospital management of convulsive status found a greater efficacy of the combination of a BZD (DZP 10mg or CLZ 1mg) with a non-sedating AED (fosphenytoin 30 mg/kg or VPA 30mg/kg) than a BZD alone (Aranda et al., 2010). The drugs combination was effective in 70% of patients whereas BZD alone stopped the seizures in only 30% of cases. According to the authors of this study, their findings emphasize the need for early use of a long-acting agent other than BZD.

3.2 Conclusion

Immediate combined polytherapy for SE has not been studied sufficiently to recommend its use. There are however some clues that early combined treatment may be useful.

4. Current guidelines and practice for SE first line therapy

4.1 Current guidelines

Both the American (Brophy et al., 2012) and European (Meierkord et al., 2010) guidelines recommend a stepwise treatment. The US recommendation propose to change the traditional "1st, 2nd, 3rd,… line of treatment", to "emergent initial therapy", "urgent control therapy" and "refractory therapy", which reflect more the need for urgent SE control (Brophy et al., 2012). BZD are recommended as "emergent initial therapy" for all patients. Because of the available evidence, LZP 0.1 mg/kg is recommended for iv, and MDZ 10 mg for im treatment. Then, an "urgent control therapy" is recommended for all patients, except when the definite underlying cause has been identified and successfully addressed, such as severe hypoglycemia for example. The second treatment aims to maintain seizure control when BZD were successful, or to stop seizures if the first line failed. The guideline states that there is a disagreement regarding the most effective drug in this setting, due to the lack of available evidence; iv PHT or fosPHT, VPA, LEV, PB or (even) MDZ in continuous infusion are however proposed for the second step of treatment. The "urgent control" therapy should rapidly follow the first line, but there is no mention of a combined initial treatment. The European guidelines published before the RAMPART study (Meierkord et al., 2010), recommend iv LZP as a first choice, or a combination of DZP 10 mg and PHT 18mg/kg, in line with the VA cooperation study (Treiman et al., 1998) if LZP is not available.

4.2 Clinical practice

In a SE management survey fifteen academic centers across the US were asked to retrospectively reported their practice on the 10 to 20 last patients treated for SE in their own institution (Cook et al., 2012). Three quarters of patients received a BZD (mainly LZP) as first line therapy, followed by PHT in 8.7% of patients. Of note, there is no mention of a combined first line therapy. Polytherapy used as initial therapy was not mentioned either in two SE

management practice surveys based on hypothetical case (Claassen et al., 2003), (Riviello et al., 2013), but it is important to remind that the questions asked in the survey didn't evoke any combined therapy. Finally, the rate of success of first line therapy in observational studies is lower than reported in controlled trials (Aranda et al., 2010), (Alvarez et al., 2011), (Cook et al., 2012), (Rantsch et al., 2013), probably reflecting the common practice of a rapid second line treatment administration without waiting for first line failure to control the seizures.

5. Special considerations

It is commonly agreed that SE requires a rapid and effective treatment. There are several class I studies pointing that BZD should be used initially; it seems also important to prevent seizures recurrence by administering a "second line" or "urgent control therapy" (Brophy et al., 2012). There are however not enough data to recommend a specific combined therapy in all patients. Moreover, some clinical situations require particular considerations.

5.1 Specific clinical situations

Alcohol withdrawal represents a frequent cause of SE (Aminoff and Simon, 1980), (DeLorenzo et al., 1996) and PHT is not effective in this setting (Kosten and O'Connor, 2004). BZD treatment and thiamine administration are required (Mayo-Smith, 1997). VPA may reduce symptoms of alcohol withdrawal and thus could be considered additionally (Kosten and O'Connor, 2004). Also, BZD withdrawal can induce SE and, logically, its treatment requires a prolonged gradual weaning of a benzodiazepine with a long half-life (Leach et al., 2012) and not a non-sedating AED. The same considerations apply for SE due to severe disturbances of glycaemia (hyper- or hypo-): a tight glucose level control is required, rather than further AED (Beleza, 2012).

PHT is one of the recommended (Brophy et al., 2012), (Meierkord et al., 2010) and, at least historically, the most widely used drug after BZD administration (Cook et al., 2012). However it may aggravate seizure in genetic generalized epilepsies (also known as idiopathic generalized epilepsies) with absence and myoclonic seizures (Benbadis et al., 2003) and even precipitate SE (Thomas et al., 2006). PHT should therefore not be used in this population, where VPA is the drug of choice after BZD administration (Wheless, 2003). LEV is also an effective treatment in genetic generalized epilepsies (Berkovic et al., 2007), but its role in SE in this population has not been studied.

Finally PHT and VPA should be used with caution in patients with hepatic disease (Asconapé, 2014) or with premorbid polypharmacy (Asconapé, 2002), because of possible medical interactions. LEV or lacosamide (LCM) are however safe in patient with hepatic diseases, and are almost devoid of relevant pharmacokinetic interactions.

6. Proposed approach and conclusion

A "one fits all" solution applying for all SE patients does not exist, reflecting the marked heterogeneity in terms of etiologies, ages and medical comorbidities. The answer to the question proposed in the title is still open, if one considers evidence-based approaches. However, there is a clear evidence to recommend the use of BZD as an immediate treatment, and to suggest considering a second, non-sedating drug to maintain or achieve seizure control. Waiting for possible future evidence regarding initial combined polytherapy, we propose here an algorithm (**Figure 1**) of early seizure treatment in SE based on the above discussion.

Well designed randomized studies are required to outline the better way to treat these patients in the early phase and some ongoing studies (Navarro et al., 2011), (Bleck et al., 2013) will hopefully provide soon precious information in this sense.

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Figure 1: Proposed rational algorithm for early seizure management in status epilepticus in adults

First treatment
Immediately

In-hospital: Intravenous lorazepam 0.1 mg/kg, midazolam 0.15 mg/kg or clonazepam 0.015 mg/kg
or
Pre-hospital: Midazolam 10 mg intramuscular

Rapid clinical assessment

Severe glycemic disturbances

EtOH or BZD withdrawal

Not in a setting of severe glycemic disturbances nor EtOH withdrawal

No available information

History of I/GGE

De novo SE or history of epilepsy other than I/GGE

No history of hepatic disease and no multiple premorbid drugs

History of Hepatic disease

Multiple premorbid treatment (drug interaction)

Rapid second treatment

Glucose level control

Further BZD treatment
+
iv thiamine if EtOH

VPA 20-30 mg/kg iv

PHT/fPHT 20 mg/kg iv
or
VPA 20-30 mg/kg iv

LEV 20-30 mg/kg iv