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Authors: Alvarez V, Januel JM, Burnand B, Rossetti AO

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Second-line status epilepticus treatment:

Comparison of phenytoin, valproate and levetiracetam

Vincent Alvarez MD[1], Jean-Marie Januel MPH RN[2], Bernard Burnand MD[2],

and Andrea O. Rossetti MD[1]

[1] Department of Clinical Neurosciences, [2] Centre of Clinical Epidemiology, Institute of Social and Preventive Medicine, Centre Hospitalier Universitaire Vaudois and Université de Lausanne, Switzerland

Address correspondence to:

Dr Andrea O. Rossetti

Département des Neurosciences Cliniques

Service de Neurologie

CHUV BH-07

CH-1011 Lausanne, Switzerland

Phone: +4121 314 12 20

Fax: +4121 314 12 90

E-mail : andrea.rossetti@chuv.ch

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Summary

Purpose: Phenytoin (PHT), valproic acid (VPA), or levetiracetam (LEV) are commonly used as second-line treatment of status epilepticus (SE), but comparative studies are not available.

Methods: Among 279 adult SE episodes identified prospectively in our tertiary care hospital over four years, we retrospectively identified 187 episodes in which PHT, VPA or LEV were given after benzodiazepines. Patients with post-anoxic SE were not included. Demographics, clinical SE features, failure of second-line treatment to control SE, new handicap and mortality at hospital discharge were assessed. Uni- and multivariable statistical analyses were applied to compare the three agents.

Key findings: Each compound was used in about one third of SE episodes. VPA failed to control SE in 25.4%, PHT in 41.4% and LEV in 48.3% of episodes in which these were prescribed. A deadly etiology was more frequent in the VPA group, while SE episodes tended to be more severe in the PHT group. After adjustment for these known SE outcome predictors, LEV failed more often than VPA (OR 2.69; 95% CI: 1.19 - 6.08); 16.8% (95% CI: 6.0% - 31.4%) of second-line treatment failures could be attributed to LEV. PHT was not statistically different from the other two compounds. Second-line treatment did not seem to influence new handicap and mortality, while etiology and the SE Severity Score (STESS) were robust independent predictors.

Significance: Even without significant differences on outcome at discharge, LEV seems less efficient than VPA to control SE after benzodiazepines. A prospective comparative trial is needed to address this potentially concerning finding.

Status epilepticus (SE) represents a severe condition with significant mortality and morbidity (Coetaux et al., 2000; Knake et al., 2001; Vignatelli et al., 2003), and its timely treatment is indicated to prevent potentially deleterious complications (Lowenstein & Alldredge, 1998). Unfortunately, high-level evidence is only available for the first-line medication; in particular, lorazepam has been shown to be more effective than phenytoin (PHT) or placebo (Trieman et al., 1998; Alldredge et al, 2001); therefore, intravenous benzodiazepines are recommended as initial approach (Meierkord et al., 2010). However, since first-line therapy fails to control at least 35-45% of patients with SE (Trieman et al., 1998), additional treatments are needed, for whom convincing evidence is lacking. Historically, PHT (Pilz & Dreyer, 1969; Wallis et al., 1968) has been used before valproic acid (VPA) (Sinha et al., 2000; Trinka, 2009) as a second-line agent. The Veteran Affairs study (Trieman et al., 1998) together with other smaller series (Misra et al., 2006; Gilad et al., 2008) showed that PHT is useful as first-line therapy, but comparative investigations using those compounds as second-line treatment after benzodiazepines are very scarce. A small prospective randomized study (Agarwal et al., 2007) analyzed PHT and VPA after diazepam failure and showed that both drugs were surprisingly highly effective (controlling SE in 88% and 84 % of patients, respectively). More recently, levetiracetam (LEV) (Rossetti et al., 2006a; Knake et al., 2008) and, to a much more limited extent, lacosamide (Kellinghaus et al., 2011) have also been described for this indication, but again without any comparison to other agents.

To address this relevant lack of information, we used our SE database to investigate the relative role of PHT, VPA and LEV in the treatment of SE as second-line agents. We did not consider lacosamide, as it was marketed in Switzerland only in September 2009, while all other drugs were available before 2006.

Methods

Patients and procedures

We retrospectively analyzed data from a prospective registry including all patients treated at our center (tertiary hospital) over four years for SE, between April 1st 2006 and March 31 2010. Details on the registry were recently published in another study (Novy et al., 2010). Briefly, SE was defined as the continuous occurrence of seizures for more than five minutes, or repeated epileptic seizures without intercurrent baseline recovery. Seizures were diagnosed clinically, but formal EEG confirmation was required for non-convulsive episodes. SE episodes were identified and screened by our neurological consultants at the emergency unit and intensive care unit, and by the EEG staff. Subjects younger than 16 years old and patients with post-anoxic SE were not included. We indentified all SE episodes in which a second-line treatment was prescribed.

Our protocol to treat SE starts with intravenous benzodiazepines (clonazepam 0.015 mg/kg or lorazepam 0.1 mg/kg), followed by a choice of PHT 20 mg/kg, VPA 20 mg/kg or LEV 20 mg/kg; all are relayed by maintenance dosages (typically, 300-400 mg PHT, 1000-2500 mg VPA, or 1000-3000 mg LEV daily). The second-line treatment is typically administered within 1-30 minutes following benzodiazepines. The vast majority of these drugs are given intravenously. Every case is discussed within 48 hours with one of both senior epileptologist of our center to guide SE treatment after the application of the initial algorithm.

Variables

Age, gender, history of previous seizures, seizures type (partial versus generalized), consciousness before treatment institution, treatments, and SE etiology were recorded prospectively. Consciousness was categorized as alert/confuse/somnolent versus stuporous/comatose. For each patient, a validated SE severity score (STESS) was calculated (Rossetti et al., 2008) and its scores categorized in ≥ 3 or < 3 (Table 1). Etiology was considered “deadly” if leading to death if not

specifically treated, as previously described (Rossetti et al., 2006b), including: massive ischemic and hemorrhagic stroke, primary or secondary cerebral tumor, CNS infection, severe autoimmune disease, AIDS with CNS complication, metabolic disturbance sufficient to cause coma, eclampsia, and sepsis. We also categorized etiology as acute vs. non-acute (Commission on Epidemiology and Prognosis, ILAE, 1993). The primary outcome was the failure of the second-line treatment, defined as the need to introduce a further compound to control SE. We considered SE as controlled if no change in antiepileptic medication was needed for at least 48 hours after clinical and electrographical resolution. We developed a specific multilevel variable to define second-line treatment, where each compound represented one level of the variable (VPA being the reference, the second level was PHT, and the third was LEV). We also prospectively recorded, at hospital discharge, mortality (calculated using patients instead of episodes as denominator), new handicap (failure to return to baseline clinical conditions), or return to baseline.

Statistical analyses

Comparisons among the three treatment groups were performed using two-tailed Fisher exact, χ^2, or ANOVA tests, as required. In order to adjust the results for possible confounders, variables with $p<0.2$ were entered in stepwise logistic regressions using the outcome as dependent variable; goodness of fit was evaluated using a χ^2 test. The population attributable fraction (PAF) of failure of the second-line treatment when using the worst acting agent was calculated using the formula (Miettinen, 1974; Hanley 2001):

[Prevalence of patients exposed to the second-line treatment in the failure cases] x [(Odds Ratio-1)/Odds Ratio]

To perform a multivariate analysis and generate an adjusted estimate of the PAF of failure of the second-treatment, we determined the PAF for multiple levels of exposure defined as above.

Results

We indentified 198 SE episodes (representing 71% of 279 episodes in our database), occurring in 167 patients, during which BZD were followed by a second-line agent. Only 8 episodes (4%) lasted less than 30 minutes. While in eleven episodes other oral agents were prescribed after failure of BZD (3 received carbamazepine, 3 pregabaline, 2 lamotrigine, 2 gabapentin and 1 phenobarbital), analysis was restricted to the 187 episodes in which PHT (70 episodes, 37%), VPA (59 episodes, 32%), or LEV (58 episodes, 31%) were used as second-line agents.

An overview of the treatment groups is presented in Table 2; several potentially important differences were observed. In the unadjusted analysis, patients treated with VPA had fewer unfavorable outcomes than the other two groups (failure of second-line agent, p=0.032; new morbidity or death, p=0.011; mortality, p= 0.045). VPA failed to control the SE in 25.4%, PHT in 41.4% and LEV in 48.3%. In the eleven subjects who received others agents, this corresponded to 28% (3/11).

Patients with a deadly etiology ($p < 0.001$) and an acute etiology (p=0.035) were more frequent in the LEV and PHT groups than in the VPA group, and subjects treated with VPA and LEV tended to have less severe SE episodes than patients of the PHT group (p = 0.007). The constitutive variables of the STESS (severe consciousness impairment, convulsive seizure, lack of previous seizures, higher age) were more frequently represented in the PHT group, except for age. Of note, treatment was started within an hour of symptoms onset in 48.5% of patients in the PHT, 30.5% in the VPA, and 29.5% in the LEV group (p= 0,03, χ^2; the difference between VPA and LEV being not significant). Discrepancies in SE severity and etiology may have played a major role regarding the outcomes; therefore, a multivariable approach was applied.

Logistic regression analyses were performed for the three outcomes, using VPA as the reference treatment (table 3). All models showed an acceptable to excellent goodness of fit (second-line treatment failure: p=0.89; new morbidity or mortality: p=0.38; mortality: p=0.21). After

adjustments for SE severity and etiology, LEV was still related to a higher risk of second-line treatment failure as compared to VPA, (OR 2.7, 95% CI 1.2 - 6.1). Treatment failures (PAF) attributable to the use of LEV corresponded to 16.8% (95% CI 6.0 – 31.4 %), suggesting that 16.8% of second-line medication failures might have been avoided using VPA instead of LEV. PHT did not differ significantly from the other two compounds.

On the other side, the choice of the second-line treatment did not influence mortality and persistent morbidity at discharge (Table 3), while a STESS score ≥3 and a deadly etiology for the SE were strongly predictive for unfavorable outcome.

Discussion

As opposed to the few comparative studies investigating the administration of VPA and PHT in SE (Mirsa et al., 2006; Gilad et al., 2008; Agarwal et al., 2007), which despite several methodological pitfalls suggest that these compounds are broadly comparable, LEV has not been tested against any other antiepileptic drug so far. This observational study suggests that the agent administered after benzodiazepines in patients with SE may influence the immediate treatment success, but not the outcome at hospital discharge: LEV seems to bear a higher risk of immediate treatment failure as compared to VPA, with 16.8% of treatment failures attributable to LEV, with PHT being in between.

It exists a paradox in the SE treatment, since practical and financial issues, and the position taken by regulatory authorities, render a prospective trial extremely difficult. A physician can chose among VPA, PHT, LEV and even other compounds, in an almost complete absence of rational evidence, but can not collect information to determine efficacy without getting informed consent from the patient, which in an emergency condition is extremely difficult. In order to attenuate the lack of

information in this field, we therefore used a sort of "natural experiment", analyzing the real-world use of these compounds in SE and their efficacy,

In this cohort, PHT was prescribed slightly more often as a second-line drug, probably because of the historical experience with this substance (Pilz & Dreyer, 1969; Wallis et al. 1968); however, VPA and LEV were each used in almost 30% of episodes. This likely reflects clinician's preferences to these compounds in situations where local or cardiac toxicity of PHT (Craig, 2005), or the risk of pharmacokinetic interactions with PHT and VPA, might be at play (Knake et al., 2008).

While treatment success rates after VPA were higher as compared to PHT and LEV in the univariate analysis, only the difference between VPA and LEV persisted after adjustment for etiology and SE severity (including age), two major predictors of SE outcome (Towne et al., 1994; Logroscino et al, 1997). Interestingly, the success rate among the 11 patients treated with other compounds was similar to that of VPA. It is unlikely that the observed differences resulted from systematic discrepancies in the loading or maintenance dosage of the second-line compounds. Actually, VPA was rather low-dosed in our hospital as compared to other series (Misra et al., 2006) and the most recent European guidelines (Meierkord 2010), whereas PHT was given as recommended by the European guidelines (Meierkord 2010); LEV was administered as previously reported in other centers (Knake et al. 2008; Berning et al., 2009) and the European guidelines (Meierkord 2010), where loading doses of at least 1000 mg and maintenance doses of about 2000 mg are described. Furthermore, escalating LEV dosage beyond 3000 mg/day has not been shown to provide any additional benefit (Rossetti et al., 2006a). The fact that LEV was given orally in few subjects before its intravenous availability (June 2007) may theoretically have slowed its action; however, this occurred in only two patients, and they responded to the treatment; in fact, previous reports describe a definite effect after oral administration in SE (Rossetti et al., 2006a).

STESS and deadly etiology were robust predictors for outcome at discharge, independently of the type of second-line treatment. This reflects convergent information from several studies (Rossetti et al., 2006b; Towne et al., 1994; Logroscino et al., 1997), and suggests that various factors contribute to SE prognosis more than the specific antiepileptic therapy. In fact, differences in immediate SE control following the second-line drug might be "compensated" by the subsequent agent, suggesting that if the SE episode is *per se* treatable, it will respond to another drug. Again, it is tempting to assume that the biological background represents the major prognostic determinant (Rossetti et al., 2006b; Towne et al., 1994).

Our study has some limitations. Although we used a prospective database, data analysis was performed retrospectively for the purpose of this evaluation, and the treatment allocation was not randomized; therefore, we cannot exclude confounding factors. However, multivariable analyses were used to control for the most important known outcome predictors, including the STESS and the etiology; moreover, there was no significant difference in treatment delay between VPA and LEV. Less important predictors could not be assessed. These include adequacy of initial treatment with BZDs, duration of SE and timing of administration of second-line drugs. We did not specifically assess missed patients from the registry, but since in our hospital all subjects with a first seizure or SE suspicion have a neurological consultation and an EEG, it is relatively unlikely that problems with case ascertainment had major influence on the results of this study. In our database, a second-line treatment was given more frequently (198/279 episodes = 70%) as compared to the first-line failure rates in published trials (35% for lorezapam (Lowenstein et al., 1998), 40% for lorazepam and 57% for diazepam (Alldredge et al., 2001), 22% for lorazepam and 42% for diazepam (Leppik et al., 1983). We believe that several patients received a second-line agent shortly after benzodiazepines to prevent seizure recurrence (as it is commonly performed in clinical practice), leading to an overestimation of the efficacy of the three treatments. This reflects broadly used common practice (personal communications with several European and American SE specialists), and differs from the semi-artificial trial settings. However, it is unlikely that a specific

second-line agent was administered in case of "almost controlled" SE, generating a systematic bias. Furthermore, two senior epileptologists oversaw the vast majority of the treatment strategies, rendering unlikely a prescription bias by different physicians. The fact that in our series both PHT and VPA appeared less efficacious than previously reported (Agarwal et al., 2007) probably reflects a different etiological and demographical profile (India vs. Switzerland). Finally, unfortunately our database does not allow extrapolating any estimation of specific side effects related to the analyzed treatments, nor to retrieve specific drug dosages.

In conclusion, this study, which to the best of our knowledge represents the first comparison between PHT, VPA and LEV in SE, suggests some caution in the use of LEV in this setting, pending a well-designed comparative trial. Despite several putative difficulties in patients' recruitment and organization, this approach appears clearly necessary to clarify this situation.

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Table 1: Status Epilepticus Severity Score (STESS), a favorable score is 0–2. Adapted from Rossetti et al., 2008.

	Features	**STESS**
Consciousness	Alert or somnolent/confused	0
	Stuporous or comatose	1
Worst seizure type	Simple-partial, complex-partial, absence, myoclonic*	0
	Generalized-convulsive	1
	Nonconvulsive status epilepticus in coma	2
Age	< 65 years	0
	≥ 65 years	2
History of previous seizures	Yes	0
	No or unknown	1
Total		0-6

* complicating idiopathic generalized epilepsy

Table 2: Comparison of the groups of second-line treatment and the SE epilepticus characteristics

	VPA	PHT	LEV	p (test)	Total
	N=59 (29.8%)	**N=70 (35.4%)**	**N=58 (29.3%)**		**N=187**
Deadly etiology	15 (25.4%)	39 (55.7%)	34 (58.6%)	<0.001 (χ^2)	88 (47.1%)
Acute etiology	27 (45.8%)	45 (64.3%)	39 (67.2%)	0.035 (χ^2)	111 (59.4%)
STESS ≥3	26 (44.1%)	49 (70.0%)	29 (50%)	0.007 (χ^2)	104 (55.6%)
Alert/Confus/Somnolent	28 (47.5%)	23 (32.9%)	29 (50%)	0.101 (χ^2)	70 (37.4%)
Stupor/Coma	31 (52.5%)	47 (67.1%)	29 (50%)	0.101 (χ^2)	107 (57.2%)
GCSE + NCSEC	22 (37.3%)	41 (58.6%)	17 (29.3%)	0.002 (χ^2)	80 (42.8%)
No previous seizure	24 (40.7%)	48 (68.6%)	30 (51.7%)	0.006 (χ^2)	102 (54.5%)
Age: mean (SD)	64 (18.9)	57.8 (18.1)	66.1 (14.9)	0.02 (ANOVA)	62.4 (17.7)
Failure of 2nd line treatment	15 (25.42%)	29 (41.42%)	28 (48.27%)	0.032 (χ^2)	72 (38.5%)
New morbidity or death at discharge	25 (42.37%)	45 (64.28%)	39 (67.24%)	0.011 (χ^2)	109 (28.3%)
Mortality/patients	4/48 (8.4%)	17/64 (26.6%)	9/47 (19.1%)	0.045 (Fisher)	30/159 (18.7%)

GCSE= generalized convulsive status epilepticus, NCSE= nonconvulsive status epilepicus in coma, STESS= Status Epilepticus Severity Score, VPA= valproate, PHT= phenytoin, LEV= levetiracetam

Table 3: Deadly etiology, Status Epilepticus Severity Score (STESS) ≥3, PHT and LEV compared with VPA with logistic regression for the different outcomes: failure of 2nd line treatment, new morbidity or death and mortality

	OR	95% CI	p
Failure of 2nd line treatment			
deadly etiology	0.997	0.53 - 1.89	0.995
STESS ≥ 3	1.51	0.8 - 2.85	0.201
Treatment (ref VPA)			
PHT as 2nd line	1.88	0.85 - 4.14	0.119
LEV as 2nd line	2.69	1.19 - 6.08	**0.017**
New morbidity or death at discharge			
deadly etiology	3.92	1.97 - 7.88	**<0.001**
STESS ≥3	3.83	1.95 - 7.52	**<0.001**
Treatment (ref VPA)			
PHT as 2nd line	1.35	0.6 - 3.02	0.463
LEV as 2nd line	1.98	0.86 - 4.57	0.109
Mortality			
deadly etiology	3.69	1.47 - 9.3	**0.005**
STESS ≥3	3.56	1.32 - 9.61	**0.012**
Treatment (ref VPA)			
PHT as 2nd line	1.34	0.43 - 4.12	0.607
LEV as 2nd line	1.08	0.33 - 3.52	0.894

STESS= Status Epilepticus Severity Score, VPA= valproate, PHT= phenytoin, LEV= levetiracetam