Predictors and prognosis of status epilepticus treated with intravenous sodium valproate

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ABSTRACT

Objective. To retrospectively review the efficacy of intravenous sodium valproate (VPAiv) treatment of status epilepticus (SE) and analyse predictive factors for seizure control and death.

Methods. Patients were included with a diagnosis of SE who had received intravenous sodium valproate (VPAiv) during 2005-2007 at Srinagarind Hospital, Khon Kaen University, Thailand. Logistic regression analysis with a stepwise approach was used to evaluate the predictors of seizure control and death.

Results. Thirty-two cases were diagnosed as SE with VPAiv treatment; 12 and 20 patients received VPAiv as the first- and second-line therapy, respectively. SE ceased in nine out of 12 patients (75%) and in seven out of 20 (35%) patients with VPAiv as the first- and second-line therapy, respectively. No serious cardiovascular compromise was recorded. The first-line therapy of VPAiv was the only factor that was significantly related to seizure control with an adjusted odds ratio [OR] of 5.571; 95% confidence interval [CI] of 1.128-27.523. Initial leukocytosis and hypotension were significantly associated with death (adjusted OR: 22.765, 95% CI: 1.176-440.640 and adjusted OR: 37.591, 95% CI: 3.035-465.571, respectively).

Conclusion. For SE patients who received VPAiv treatment, the first-line VPAiv was effective. Initial leukocytosis and hypotension were factors that correlated with death.

Key words: status epilepticus, sodium valproate, predictors, prognosis, treatment, intravenous sodium valproate

Status epilepticus (SE) is a serious neurological condition in epileptic patients. The mortality rate is high, particularly in those where the condition is undetectable or uncontrollable with brain anoxia (Chin et al., 2004; Koubeissi and Alshekhlee, 2007). Older age or underlying chronic conditions are also associated with a poor outcome (DeLorenzo et al., 1995; Lowenstein and Alldredge, 1993). It is estimated that 30 to 43 percent of patients with SE are resistant to the first two recommended drug therapies (Holtkamp et al., 2005; Mayer et al., 2002).

Sodium valproate, classified within the carboxylic acid group, has a broad anticonvulsant effect. It is now approved for the treatment of SE in Norway and Hungary (Shorvon et al., 2008). Intravenous sodium valproate (VPAiv) has been reported to be an effective treatment for SE without any serious cardiovascular side effects (Limdi et al., 2005). The contraindication for valproate use is significant hepatic dysfunction. Due to the increasing use of VPAiv treatment for SE, we therefore investigated the efficacy and prognostic factors of this treatment and predictive factors for seizure control.
Patients and methods

Study population

We retrospectively reviewed all adult patients (aged 15 years old and over) with SE who were admitted to Srinagarind hospital, Khon Kaen University, Thailand between 2005 and 2007. SE was defined using the Veterans Affairs Cooperative Study (VACS) criteria (Treiman et al., 1998). The criteria for SE were two or more generalised convulsions, without full recovery of consciousness between seizures or continuous convulsive activity for more than 10 minutes. The inclusion criterion was SE patients who were treated with VPAiv as the first- or second-line medication.

We recorded patient demographics, etiology of SE, physical signs, laboratory tests and dose of sodium valproate administration. Physical signs were based on vital signs, general examination and neurological examination. Hypotension was defined as systolic blood pressure lower than 90 mmHg and/or diastolic blood pressure lower than 60 mmHg. Baseline laboratory tests were included for complete blood count, renal function, liver function, electrolytes as well as brain computed tomography. Total white blood cells of more than 10,000 cells/mm³ or less than 4,000 cells/mm³ indicated leukocytosis and leukopenia, respectively.

The outcome of treatment analysed was seizure control and death. Seizure control was defined as the cessation of seizures by either clinical or electrical evidence. Clinically, this was determined as seizure activity that ceased within 30 minutes after taking antiepileptic medication with no additional antiepileptic medication required for at least 24 hours after cessation of seizure. Electrical seizure activity included any of the five ictal patterns described previously (Treiman et al., 1990). To evaluate side effects of sodium valproate, blood pressure and heart rate were monitored every 15 minutes in the first hour and every 30 minutes afterwards.

The treatment protocol was reviewed and approved by the institutional review board and the ethics committee of Khon Kaen University.

Data analysis

We categorized eligible patients into two groups according to outcome; seizure controlled versus seizure uncontrolled group and death versus survival group. The Wilcoxon rank sum test and Fisher’s exact test were used to compare differences in medians and proportions, respectively, for the two groups. Difference was considered significant at p < 0.05.

Baseline characteristics were compared between patients who received VPAiv as first- and second-line therapy. Univariate logistic regression analyses were used to calculate the crude odds ratios of each variable for the success of seizure control and death. All variables with p < 0.30 in univariate analysis were included in subsequent multivariable logistic regression analyses. Variables with p > 0.10 in the multivariate model were excluded by the stepwise approach. The final model retained all variables with p < 0.10. Analytical results were presented in terms of crude odds ratios (OR), adjusted OR and their 95% confidence intervals (CI). To demonstrate the discriminative power or accuracy of the model, c statistics or the area under the receiver operating characteristic (ROC) curve were tested (Hanley and McNeil, 1982).

All data analyses were performed by SAS software version 8.2 (SAS Institute Inc., Cary, NC, USA).

Results

Forty-nine cases were diagnosed as SE between 2005 and 2007. Withdrawal of antiepileptic medication was the most common cause of SE (seven patients). The other causes were head injury (five patients), brain tumour (four patients), cerebral infarction (three patients), subarachnoid haemorrhage (two patients), renal failure (two cases), intracerebral haemorrhage (one patient), alcohol-related SE (one patient), bacterial meningitis (one patient), malignancy with brain metastasis (one patient) and unknown cause (five patients). All patients exhibited convulsive SE and received 10 mg of intravenous diazepam after the continuation of seizure for 10 minutes. Out of the 49 cases, 12 (24%) and 37 (76%) patients were respectively treated with VPAiv and phenytoin as the first-line treatment. VPAiv or phenytoin were given at 15-25 mg/kg and 15-20 mg/kg, respectively with the maximal infusion rate of 50 mg/min. As a result, SE ceased in 75% of patients with VPAiv (9 patients) versus 46% (17 patients) with phenytoin (p = 0.104).

In total, 32 patients received VPAiv; 12 as first-line and 20 as second-line therapy. No serious cardiovascular compromise was found but two patients developed hepatitis. Half of the patients (16 cases) were defined as having controlled seizures with VPAiv, based on clinical evaluation for 13 and both clinical and EEG in three patients. Of those, nine received VPAiv at first-line treatment and the remaining seven as second-line -p = 0.06. For the uncontrolled seizures group, the median age was 55.5 years (range 19-77) and the dose of VPAiv administered 800 mg (range 750-1600). For the controlled seizures group, the median age was 48 years (range 20-78) and the VPAiv dose administered 800 mg (range 750-1500). The order of treatment, specifically first-line therapy, was the only factor that was significantly related to seizure control by both univariate and multivariate logistic analysis (adjusted OR: 5.571 and 95% CI: 1.128-27.523). The area under the ROC curve of the final model was 0.69.

Data on overall outcome was available for 31 patients. From the 17 (54.8%) that died VPAiv was administered
as first-line therapy in 5 and as second-line therapy in 12. For this group, the median age was 53 years (range 23-78) and the median dose of VPAiv 800 mg (range 750-1 500). The corresponding values for the 14 patients that survived were: median age 51 years (range 20-71); median dose of VPAiv 800 mg (range 750-1 600).

There were six significant variables by univariate logistic analysis (Table 1). However, only leukocytosis and hypotension remained in the multivariate final model with the adjusted OR (95% CI) of 22.765 (1.176-440.640) and 37.591 (3.035-465.571), respectively. The area under the ROC curve or the c statistic of the final model was 0.93.

Discussion

SE is a life-threatening condition that needs prompt therapeutic strategies. VPAiv has been shown to be effective for SE treatment, but the available data limit its use as a first-line medication in the treatment guidelines for SE. During 2005-2007, intravenous phenobarbital was temporarily unavailable in Thailand. For this reason, VPAiv was increasingly used as the first- or second-line therapy in our hospital setting. Despite the lack of an FDA-approved indication, an increasing number of reports support the use of VPAiv for the treatment of SE (Wasterlain and Chen, 2008). Most reports are favourable with generally mild side-effects. Misra et al. showed that VPAiv significantly prevented SE as first-line treatment when compared with i.v. phenytoin (Misra et al., 2006). However, Agarwal et al. did not find significant differences in efficacy between these two medications (Agarwal et al., 2007), although the rate of seizure control was more than 80% (88% for VPAiv and 84% for phenytoin). Another study showed the equal efficacy of VPAiv and i.v. diazepam with the success rate of 80% and 85%, respectively (Mehta et al., 2007). Even though the first-line VPAiv demonstrated a higher success rate of seizure control than the first-line phenytoin treatment (75% vs 46%, respectively), this was not statistically significant (p = 0.104). The numbers of patients may be too small to be statistically significant. VPAiv, as the first-line treatment, not surprisingly, was the only significant predictor for the cessation of seizures in convulsive SE, but did not predict mortality. Initial leukocytosis and hypotension were significantly associated with death. These two factors were associated with multi-organ failure and the systemic inflammatory response syndrome. This might imply that early recognition and prompt treatment of SE may improve survival rate, as previously reported (Treiman et al., 1998).

There was no serious cardiovascular compromise in any of the subjects but hepatic complication did occur in two patients. The small sample size and the retrospective design were limitations of the study.

In summary, for SE patients who received VPAiv treatment, the first-line VPAiv was effective and initial leukocytosis and hypotension were correlated with death. □

Acknowledgments/Disclosures.

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References


Table 1. Crude odds ratio on survival by intravenous sodium valproate using univariate logistic analysis.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Number of patients (%)</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
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<tbody>
<tr>
<td></td>
<td>Survival (n = 14)</td>
<td>Death (n = 17)</td>
<td></td>
</tr>
<tr>
<td>Abnormal renal functiona</td>
<td>1 (7)</td>
<td>9 (53)</td>
<td>14.625</td>
</tr>
<tr>
<td>Abnormal liver functionb</td>
<td>1 (7)</td>
<td>10 (59)</td>
<td>18.571</td>
</tr>
<tr>
<td>Abnormal electrolytesc</td>
<td>2 (14)</td>
<td>9 (53)</td>
<td>6.750</td>
</tr>
<tr>
<td>Leukocytosisd</td>
<td>5 (36)</td>
<td>16 (94)</td>
<td>28.800</td>
</tr>
<tr>
<td>Abnormal CT brain</td>
<td>11/12 (92)</td>
<td>7/15 (47)</td>
<td>0.080</td>
</tr>
<tr>
<td>Hypertensione</td>
<td>2 (14)</td>
<td>15 (88)</td>
<td>45.000</td>
</tr>
</tbody>
</table>

a, b, cDefined by the out of normal range of blood urea nitrogen or serum creatinine, liver function test, and electrolytes, respectively.
d Defined by white blood cell count over 10 000 cells/mm³.
e Defined as systolic blood pressure lower than 90 mmHg and/or diastolic blood pressure lower than 60 mmHg.
CT: computed tomography.


