Factors Associated with Good Seizure Control in Patients on Valproic Acid

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ABSTRACT

Objective: This study aims to generate a reference range for valproic acid (VPA) in this cohort and determine the factors associated with good seizure control in patients taking this drug.

Materials and Methods: We conducted a prospective, cohort, observational study among patients with epilepsy who received VPA treatment at Hospital Kuala Lumpur. The patients were considered to have good control if they had a 50% or higher seizure reduction in the one-year study period compared with the previous year. The VPA reference range was generated from those patients who had good control and whose drug concentration values were available. Multiple logistic regression analysis with a backward likelihood ratio method was applied to assess the predicting factors for good seizure control.

Results: A total of 242 patients were recruited and followed up for one year. The VPA reference range was determined to be 40-85 mg/L. After multivariate analysis, significant predictive variables for good control were monotherapy [adjusted OR 4.74, 95% CI: 2.258, 9.947, p<0.001], non-smoking [adjusted OR 3.23, 95% CI: 1.099, 9.473, p=0.033], normal brain imaging results [adjusted OR 5.83, 95% CI: 2.507, 13.552, p<0.001], and the absence of stress [adjusted OR 19.98, 95% CI: 9.255, 42.764, p<0.001].

Conclusion: Monotherapy, non-smoking, normal brain imaging results, and the absence of stress are predictive of good seizure control in patients on VPA. However, a serum concentration of VPA in the reference range failed to predict good seizure control.

Keywords: Valproic acid, predictors, seizure

Introduction

For many years, serum drug concentration has been used to assist physicians in the management of epilepsy. However, the early enthusiasm and widespread use of drug analysis have resulted in the inappropriate use of the therapeutic drug monitoring (TDM) service, leading to wastage and increased costs [1, 2]. To provide a more rational use of TDM, several strategies have been suggested to improve its usage. It is no longer acceptable to request TDM without pharmacological justification; instead, controlled sampling with predefined indications has been put into place, which has resulted in a reduced number of requests [3-5].

A recent review found no evidence to support the routine concentration measurement of newly diagnosed patients on monotherapy [6]. Subsequent guidelines have suggested selective, rather than routine, monitoring of drug concentrations [7, 8]. When Minshall et al. [9] considered the impact of the new guidelines, they found a significant decline in the number of drug concentration requests in centers that had adhered to this new recommendation.

In Malaysia, antiepileptic drug (AED) concentrations are monitored in almost all government hospitals [10]; however, the pattern of monitoring may vary among individual hospitals. Regarding the TDM of valproic acid (VPA), the Malaysian Guidelines on the Management of Epilepsy consider monitoring VPA serum concentration to be unhelpful in the treatment of epilepsy [11]. Interestingly, our data showed an increasing utilization of VPA, but did not show a similar trend in the number of drug concentration requests. Consideration of this has provided the background for our investigation of VPA concentration, as well as other factors that could contribute to good seizure control for our patients.
Materials and Methods

Patients
The present prospective, cohort study was undertaken at the Hospital Kuala Lumpur, Malaysia. Patients were recruited from the Epilepsy Clinic of this hospital. The inclusion criteria were: (i) patients aged 18 years old and above, (ii) those taking VPA (monotherapy or polytherapy) for at least 12 months before the recruitment started, and (iii) those who had given their informed consent. The exclusion criteria were: (i) the VPA dose being modified or discontinued during the study period, (ii) patients who were on any other drugs known to be enzyme-inducers or inhibitors, and (iii) patients who were taking traditional medicine.

Study protocol
For all patients who met the inclusion criteria, the following data were collected at the start of study: (i) demographic and socioeconomic information, (ii) disease and medication-related information, and (iii) the most recent EEG and brain images (i.e., CT/MRI). A seizure diary was used to record any seizure occurrences and any side effects throughout the study period. A baseline seizure frequency was retrospectively derived from the number of seizures that had occurred in the previous 12 months. A blood sample from each patient was taken on any clinic visit during the study period, for the measurement of VPA concentration. All patients were followed up for one year.

The study protocol was approved by the Malaysian Research Ethical Committee (KKM/NIH-SEC/08/0804/P10-598).

Outcome of study/Study end-point
At the end of the one-year follow-up period, the patients were categorized into good control or poor control groups. Patients were considered as good control if they had at least a 50% reduction in the number of seizures in this one-year study period compared with the previous year [12].

Statistical Analysis

Determination of the VPA reference range

Only the data of patients from the good control group were included in this analysis. Two approaches were used: the first approach was to determine the range based on mean±one standard deviation (1SD); The second approach was based on a graph that was plotted of the cumulative percentage of patients against VPA concentration to determine the lower and upper limits of the reference range [13].

Figure 1. Cumulative percentage (%) of patients in the good control group (n=76).
in the cumulative percentage of responders occurred between 54.3 and 83.8 mg/L. Subsequently, we found that 52 out of 76 patients had VPA concentrations between this range. Based on the two ranges of values obtained above, we selected the reference range to be 40–85 mg/L, which included the lower end obtained by the first method and the upper end obtained by the second method. Given this new reference range, we found that the VPA concentrations of 63 out of the 76 patients (82.9%) were within this range.

Simple logistic regression

Table 2 shows the results of the univariate analysis by simple logistic regression. All predictors were included in the preliminary final model. Some insignificant variables with clinical importance were included despite p > 0.25; these were (i) mean VPA concentration values and (ii) attainment of predetermined reference range (40-85 mg/L).

Multiple logistic regression

Preliminary final model

The preliminary final model deduced from the backward likelihood ratio method resulted in eight variables that were: age when the AED was started; monotherapy; normal brain imaging; education level; non-smoking; absence of stress; VPA concentration; and a positive family history of epilepsy. A collinearity test was performed and showed that multicollinearity did not exist. The Hosmer–Lemeshow test (p = 0.113) showed that the preliminary final model fits with the overall percentage for the classification table (91.3%) at above 80%.

Final model

These eight significant variables in the preliminary final model were further analyzed using the Enter method. The test for fitness of the final model showed that the final model fit with: (i) the Hosmer–Lemeshow test (p = 0.885); (ii) the overall percentage for the classification table (83.5%); and (iii) the AUROC (89.9%).

Discussion

VPA has an unpredictable relationship between its dose and its concentration. Therefore, there is a need to individualize and maintain therapy using TDM [7]. Although the reported range of 50 to 100 mg/L has been widely used, there are patients who achieve seizure control at lower concentrations. Patients with idiopathic generalized epilepsy have shown a good response at lower doses and concentrations [16-19]. We have attempted to develop a VPA reference range using our own patient data, based on the approach described by Eadie [13]. We plotted the drug concentrations against the cumulative proportion of patients treated whose seizures were fully controlled at various VPA concentrations [16-19].

Table 3 shows the significant factors associated with good control in patients with epilepsy on VPA by multiple logistic regressions. These were: (i) age when treatment with the first AED was started; (ii) VPA monotherapy; (iii) normal brain imaging result; (iv) non-smoking; and (v) absence of perceived stress.

Table 1. Characteristics of patients with epilepsy on valproic acid (n=242)

| Characteristics                      | Good control | Poor control |
|--------------------------------------|--------------|--------------|
|                                      | (n=126)      | (n=116)      |
| Age (year), mean (SD)                | 33.01 (10.24) | 35.92 (10.67) |
| Gender, n (%)                        |              |              |
| Female                               | 53 (42.1)    | 50 (43.1)    |
| Male                                 | 73 (57.9)    | 66 (56.9)    |
| Ethnicity, n (%)                     |              |              |
| Malay                                | 79 (62.7)    | 53 (45.7)    |
| Chinese                              | 24 (19.0)    | 26 (22.4)    |
| Indian                               | 21 (16.7)    | 36 (31.0)    |
| Others                               | 2 (1.6)      | 1 (0.9)      |
| Highest level of education*, n (%)   |              |              |
| College/University                   | 13 (10.3)    | 6 (5.2)      |
| Secondary                            | 98 (77.8)    | 89 (76.7)    |
| Primary                              | 15 (11.9)    | 21 (18.1)    |
| Family support status, n (%)         |              |              |
| Yes                                  | 89 (70.6)    | 58 (50.0)    |
| No                                   | 37 (29.4)    | 58 (50.0)    |
| Marital status, n (%)                |              |              |
| Yes                                  | 23 (18.3)    | 27 (22.3)    |
| No                                   | 103 (81.7)   | 89 (76.7)    |
| Employment status, n (%)             |              |              |
| Yes                                  | 49 (38.9)    | 28 (24.1)    |
| No                                   | 77 (61.1)    | 88 (75.9)    |
| Active smoker, n (%)                 |              |              |
| Yes                                  | 11 (8.7)     | 24 (20.7)    |
| No                                   | 115 (91.3)   | 92 (79.3)    |
| Age at diagnosis (year), mean (SD)   | 19.93 (8.46) | 21.80 (9.75) |
| Seizure type, n (%)                  |              |              |
| Generalized                          | 103 (81.7)   | 37 (31.9)    |
| Partial                              | 14 (11.1)    | 43 (37.1)    |
| Secondarily generalized              | 9 (7.2)      | 36 (31.0)    |
| Etiology, n (%)                      |              |              |
| Known                                | 20 (15.9)    | 56 (48.3)    |
| Unknown                              | 57 (45.2)    | 28 (24.1)    |
| Undocumented                         | 49 (38.9)    | 32 (27.6)    |

Family history of epilepsy, n (%)     | 26 (20.6)    | 40 (34.5)    |
No                                    | 100 (79.4)   | 76 (65.5)    |
Age when first AED started, mean (SD)  | 20.21 (8.39) | 22.34 (9.94) |
Age when VPA started, mean (SD)        | 23.02 (8.65) | 25.90 (9.78) |
Duration on VPA (year), median (IQR)   | 4 (4)        | 4 (4)        |
First AED prescribed, n (%)            |              |              |
VPA                                   | 85 (67.5)    | 37 (31.9)    |
PHT                                   | 24 (19.0)    | 42 (36.2)    |
CBZ                                   | 11 (8.7)     | 31 (26.7)    |
Others                                | 6 (4.8)      | 6 (5.2)      |
Current AED regime, n (%)              |              |              |
Monotherapy                           | 78 (61.9)    | 32 (27.6)    |
Polytherapy                           | 48 (38.1)    | 84 (72.4)    |
VPA dose (mg/day), mean (SD)           | 760.32 (335.64) | 886.21 (349.14) |
VPA concentration** (mg/L), mean (SD) | 60.71 (18.06) | 61.35 (26.07) |
VPA range, n (%)                      |              |              |
Not within 40–85 mg/L                  | 13 (17.1)    | 14 (18.4)    |
Within 40–85 mg/L                     | 63 (82.9)    | 62 (81.6)    |
EEG, n (%)                            |              |              |
Normal                                | 96 (76.2)    | 21 (18.1)    |
Abnormal                              | 30 (23.8)    | 95 (81.9)    |
Brain imaging result                   |              |              |
Normal                                | 109 (86.5)   | 68 (58.6)    |
Abnormal                              | 17 (13.5)    | 48 (41.4)    |

*Secondary education is equivalent to GCE A levels. Primary education refers to elementary school up to age 12 years; † VPA level refers to 76 patients in both groups; ‡Expressed in Median (IQR); §Refers to predetermined reference range (40-85 mg/L); AED: antiepileptic drug; VPA: valproic acid
vious findings that treatment should not focus on achieving a concentration in the reference range. This method was implemented by the Italian TDM Study Group in Epilepsy [20], where each patient’s dose was titrated to achieve concentrations within the target range. The study by this group found that this approach did not improve the overall seizure outcome.

The significant predictors to good seizure control in patients with epilepsy on VPA that were identified in our study were monotherapy, non-smoking, normal brain image (MRI or CT) results, and an absence of stress. Our study showed that patients who were on VPA monotherapy were five times more likely to have a favorable outcome. Monotherapy is more likely to be observed in newly diagnosed patients or in patients with less severe conditions [21]. In the present study, the mean age of diagnosis between the two groups was not significantly different. However, there were more patients on polytherapy in the poor control group (i.e., 72% vs. 38%). Previous studies have shown that use of a greater number of AEDs is found among patients with poor seizure control [22, 23].

Another predictive factor of seizure outcome with an obscure mechanism is non-smoking behavior. In this study, we found that patients who did not smoke were three times more likely to achieve good seizure control compared with those who smoked. Maternal cigarette smoking has previously been associated with an increased risk of seizures in children [24, 25]. Among adults, Dworetzky et al. [26] found a two-fold increase in risk of seizures in current smokers compared with non-smokers. Our findings support that cessation of smoking may be an effective means of achieving good seizure control in patients with epilepsy on VPA. In animal models, nicotine has been found to diminish the anticonvulsant activities of VPA and other AEDs [27]. Further research needs to be carried out to explore the effect of smoking cessation on seizure outcome.

We found that patients with normal brain imaging results were approximately six times more likely to achieve good seizure control. Abnormal brain image, such as MRI or CT, results have been associated with an increased risk of seizure recurrence [28]. Additionally, a higher risk of seizure recurrence has been reported in patients with intractable epilepsy [29-31]. In our study, also, abnormal findings occurred significantly more often in the poor control group of patients.

The absence of stress is associated with an approximately 20 times better chance of a favorable outcome. In this study, more than 80% of

| Table 2: Univariate analysis of predicting factors for good seizure control (n=242) |
|------------------|-----------------|-----------------|--------------|
| Variables         | Crude Odds Ratio | 95% CI          | p*           |
| Age (year)       | 0.974           | 0.950-0.998     | 0.033        |
| Age at diagnosis (year) | 0.977       | 0.950-1.005     | 0.112        |
| Age when AED started (year) | 0.975      | 0.948-1.002     | 0.073        |
| Age when VPA started (year) | 0.967      | 0.940-0.994     | 0.017        |
| VPA dose (mg/day) | 0.999           | 0.998-1.000     | 0.006        |
| Mean VPA concentration (mg/L) | 0.996     | 0.978-1.014     | 0.651        |
| No. of side effects | 0.388         | 0.265-0.567     | <0.001       |
| Ethnicity         |                |                 |              |
| Malay             | 1              |                 |              |
| Chinese           | 0.619           | 0.322-1.192     | 0.152        |
| Indian            | 0.391           | 0.206-0.743     | 0.004        |
| Others            | 1.342           | 0.119-15.730.812|              |
| Educational level |                |                 |              |
| Primary           | 1              |                 |              |
| Tertiary          | 3.033           | 0.939-9.798     | 0.064        |
| Secondary         | 1.542           | 0.749-3.174     | 0.240        |
| Family support status |            |                 |              |
| No               | 1              |                 |              |
| Yes              | 2.405           | 1.418-4.081     | 0.001        |
| Employment status |                |                 |              |
| No               | 1              |                 |              |
| Yes              | 2.000           | 1.147-3.487     | 0.015        |
| Active smoker     |                |                 |              |
| Yes              | 1              |                 |              |
| No               | 2.727           | 1.270-5.858     | 0.010        |
| Seizure type      |                |                 |              |
| Secondarily generalized |        |                 |              |
| Generalized       | 11.135          | 4.898-25.317    | <0.001       |
| Partial           | 1.302           | 0.505-3.358     | 0.585        |
| Etiology          |                |                 |              |
| Known            | 1              |                 |              |
| Unknown           | 5.700           | 2.882-11.275    | <0.001       |
| Stress preceding seizure |        |                 |              |
| Yes              | 1              |                 |              |
| No               | 16.587          | 8.782-31.331    | <0.001       |
| No. of seizures before treatment initiated |           |                 |              |
| >10              | 1              |                 |              |
| ≤10              | 5.256           | 2.859-9.663     | <0.001       |
| Family history of epilepsy |        |                 |              |
| Yes              | 1              |                 |              |
| No               | 2.024           | 1.137-3.604     | 0.017        |
| History of febrile seizure |        |                 |              |
| Yes              | 1              |                 |              |
| No               | 1.412           | 0.835-2.389     | 0.198        |
patients who reported experiencing stress had poor seizure control. Stress was reported to be as a result of sleep deprivation, fatigue, loss of financial income, and life problems. A substantial number of our patients reported that the frequency of their seizures increased when they experienced stress. Previous studies have shown that stress is among the most frequently self-reported precipitants of seizures in patients with epilepsy [32-34], which can be triggered by physical or emotional factors. Stress does not only increase the number of seizures in patients with epilepsy [35, 36], but has also been reported to induce de novo seizures [37].

In conclusion, we have determined VPA concentrations between 40-85 mg/L to be the reference range in our patients, but having a serum concentration in the reference range did not predict good seizure control. This study suggests that predictors of good seizure control in patients on VPA are monotherapy, non-smoking, normal brain imaging results, and the absence of stress.

**Table 2. Univariate analysis of predicting factors for good seizure control (n=242) (continue)**

| Variables          | Crude Odds Ratio | 95% CI         | p*  |
|--------------------|------------------|----------------|-----|
| AED naive          |                  |                |     |
| No                 |                  |                |     |
| Yes                | 4.426            | 2.580-7.594    | <0.001 |
| VPA range          |                  |                |     |
| Not within range   | 1                |               |     |
| 40-85 mg/L         | 1.094            | 0.476-2.515    | 0.832 |
| AED regime         |                  |                |     |
| Polytherapy        | 1                |               |     |
| Monotherapy        | 4.266            | 2.478-7.343    | <0.001 |
| EEG result         |                  |                |     |
| Abnormal           | 1                |               |     |
| Normal             | 14.476           | 7.744-27.062   | <0.001 |
| Brain imaging result |              |                |     |
| Abnormal           | 1                |               |     |
| Normal             | 4.526            | 2.409-8.504    | <0.001 |

*pSimple logistic regression test
AED: antiepileptic drug; VPA: valproic acid

**Table 3. Multivariate analysis of predicting factors for good seizure control (n=242)**

| Variable                      | Adjusted Odds Ratio | 95% CI         | p  |
|-------------------------------|---------------------|----------------|----|
| Age when AED was started (year) | 0.957               | 0.920-0.995    | 0.027 |
| On monotherapy                | 4.739               | 2.258-9.947    | <0.001 |
| Normal brain imaging          | 5.829               | 2.507-13.552   | <0.001 |
| Non-smoking                   | 3.227               | 1.099-9.473    | 0.033 |
| Absence of stress             | 19.984              | 9.253-42.764   | <0.001 |

Constant: -3.373. The model fits reasonably well. There were no interaction and multicollinearity problems.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the ethics committee of Malaysian Research Ethical Committee (KKM/NIHSEC/08/0804/P10-598).

**Informed Consent:** Informed consent was obtained from the patients who participated in this study.

**Peer Review:** Externally peer-reviewed.

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