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Apparent Clearance of Valproic Acid in Patients with Mania Associated with Bipolar Disorders in Sarawak General Hospital and Sentosa Hospital

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ABSTRACT

Introduction: Valproic acid (VPA) is one of the medication options for patients with bipolar disorder. Dose initiation can be based on estimated patient clearance of 7-12ml/kg/hr. Patients with mania associated with bipolar disorder were found to have a higher clearance compared to patients with epilepsy, hence the estimated clearance may not be accurate in this patient population. This study aimed to investigate the population clearance value of valproic acid in patients with mania associated with bipolar disorder in Sarawak General Hospital (SGH) and Sentosa Hospital.

Methods: This retrospective study entailed extraction of data from Therapeutic Drug Monitoring (TDM) request forms received from both hospitals in the year 2017. Included patients were stabilized for 3 months on VPA monotherapy for their mania, not on concurrent medication which can affect the clearance of VPA, no renal and hepatic impairments and claimed to be compliant. Clearance was calculated based on the formula Clearance (L/hr) = [VPA dose(mg)]/[Clearance at steady state (Css) measured (mcg/ml) x Interval (hr)]. Both salt factor and bioavailability were assumed to be 1.0 except for sustained release tablet which was 0.9. Clearance difference between

gender was analysed using Independent t-test. Correlation was measured by Pearson correlation test to analyse the correlation between clearance and the age, weight and dose.

Results: A total of 67 samples were taken. Mean age, weight and dose were 41.1 years (SD 14.86), 67.0kg (SD 16.10) and 1037mg (SD 395.75) respectively. The mean clearance (Cl/F) was found to be 9.20ml/kg/hr (SD 4.19). A negative but weak correlation (r=-0.29) was found between the weight (kg) and mean clearance (Cl/F) of patients (p=0.02).

Conclusion: Localised population clearance values enable a more precise dose recommendation for patients on VPA therapy for mania associated with bipolar disorder. A statewide study on VPA pharmacokinetic profile in this patient population is recommended to be performed to further validate the clearance value, enabling optimal dosing of VPA during initiation of treatment.

Keywords: Valproic acid, population clearance value, therapeutic drug monitoring, mania, bipolar disorder

INTRODUCTION

Valproic acid (VPA) is a carboxylic acid-derived anticonvulsant that is currently used to treat epilepsy, bipolar disorder, schizophrenia, and prevention of migraine headaches (1). The mechanism of action of VPA is not well understood. VPA is thought to restore the balance of certain natural substances (neurotransmitter) in the brain (1). VPA is used in bipolar disorder usually to augment the effect of antipsychotic drugs or mood stabilizers such as lithium. VPA augments gamma-aminobutyric acid-ergic (GABA)-ergic function by increasing the release of gamma-aminobutyric acid, decreasing the catabolisation and through the increase in the density of type B GABA receptors. In addition, VPA causes the blockade of voltage-gated sodium channels (2).

VPA is available in tablet (immediate-release, enteric coated or sustained release), syrup, and intravenous formulations. The recommended dosage of VPA in bipolar disorder for initial dosing is 20mg/kg for mania and followed by dose adjustment in the next 3 to 5 days (3). As an alternative, VPA can be prescribed as 500mg to 700mg daily in divided dose, which can then be increased by 30.0% to 50.0% every 2 to 3 days as tolerated (3). For maintenance therapy, 1000mg to 3000mg per day once daily dosing or twice daily dosing is recommended (3). In cases of hypomania, lower dosage can be used (3). However, VPA has a narrow therapeutic index in which a slight increase in the dose can cause toxicity.

The accepted therapeutic range for treatment of bipolar disorder, anxiety, depression, psychosis, substance-abuse withdrawal, and other behavioral disturbances is 50 to 125mcg/ml (4). Most patients experience therapeutic effect without excessive side effects within the therapeutic range. Toxicity may happen if the drug level is greater than 175mcg/ml which can be associated with coma, stupor, and CNS toxicity (5). Therefore, VPA level needs to be monitored to ensure optimised therapeutic effect for each individual patient.

To date, there is not much research done globally or in Malaysia to investigate the pharmacokinetic data of VPA in psychiatric patients. A research was done in Iran to compare the VPA clearance between epileptic patients and acute manic patients. It was a prospective study that consists of 25 epileptic patients diagnosed via Electroencephalogram (EEG) and 19 manic patients diagnosed

according to Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria (6). Results showed that clearance of VPA in manic patients was significantly higher in acute manic patients compared to epileptic patients (10.35±5.77 vs. 7.70±2.63 ml/kg/h, *P*= 0.047) while there was no significant correlation between clearance of VPA and different gender, age nor weight (6). Two hypotheses on pharmacokinetic changes were discussed in the research paper. The first was related to the increased hepatic blood flow that led to increase in hepatic clearance while the second was related to the probable increment of volume of distribution in acutely manic patients as a result of changes in secondary messenger system and membrane transport. However, the authors concluded that VPA might be less affected by the first hypothesis as VPA has low hepatic extraction ratio 6).

In contrast, another research that was done in psychiatric and neurologic clinics of Ebn–sina and Ghaem Hospitals in Mashhad University of Medical Science in Iran showed that the clearance of VPA was not affected by total body weight, gender, age, past medical history and medication details (7). A linear pharmacokinetic model for VPA was assumed in this research where the dose was not correlated with the clearance. The result of VPA clearance not being affected by patients' age were concurred by the findings of Birnbaum et al.; however Battino et al. study and Yukawa et al. found otherwise (8,9,10).

In Thailand, a study with a population size of 206 manic patients from Somdet Chaopraya Institute of Psychiatry and Srithanya Hospital whose VPA level was routinely monitored showed that the clearance and volume of distribution were 0.464L/h and 23.3L respectively, which were concluded to be similar to those in epilepsy patients (11). However, unlike the previous studies discussed, this study showed that VPA pharmacokinetics followed one compartment model as the data collection in this study was done at the end of the dosing interval and provided little insight on the alpha phase or absorption process (11). Other than that, the author concluded that the clearance of VPA could be predicted from body weight of the patients, suggesting the association between weight and organ functionality and development for VPA clearance (11). Contradicting Mohammadpour et al., the CL/F calculated from the result of this study was 0.464L/h, which was similar to those in epileptic patients (7,11). Age remained an unclear covariate for VPA clearance in this study as the youngest patient was 18 years old. In Tanikawa et al., clearance constantly increased in a linear fashion until 12 years old and then remained constant after that (11,12). Lastly,

Methaneethorn et al. also showed co-administration of medicines such as perphenazine, trihexyphenidyl, clonazepam, risperidone, haloperidol, chlorpromazine, and lithium had significant effects on VPA clearance (11).

Thus far, few studies had been carried out to investigate the pharmacokinetic parameters of VPA for patients with mania associated with bipolar disorders. Present evidences are unclear whether VPA clearance is affected by age, gender, body weight of patient, and also the VPA dose, itself (11). Furthermore, data that is related to the Malaysian population and in Kuching specifically is lacking.

The findings obtained from this study can serve as a guide for TDM pharmacists to provide a more precise treatment recommendation for patients on VPA therapy for mania associated with bipolar disorder specific to the Malaysian population. The selection of initial dosing regimen and modification of dosing regimen can be improved with the knowledge of population specific clearance profile.

METHODS

The study was done retrospectively to determine the population clearance values of VPA in patients with mania associated with bipolar disorders in both Sarawak General Hospital and Sentosa Hospital using data retrieved from TDM requests received between January 2017 and December 2017. Convenience sampling was used in this study. The inclusion criteria were adult patient (above 18 years old) taking oral VPA (either oral solution, enteric-coated tablet, or sustained release tablets of VPA only) for mania associated with bipolar disorders or co-treatment with other drugs that have no effect on the clearance of VPA with blood samples categorised under pre-sampling (sample taken 30 minutes or just before next dose). Any patients who were non-compliant to the treatment regimens (as written in the TDM form), or having hypoalbuminemia or abnormal liver function, or end-stage renal failure were excluded. Patient on VPA therapy for psychiatric and antiepileptic management with history of diabetes, thyroid disorders, cardiovascular disease or chronic obstructive pulmonary disease (as written in the TDM form) were excluded as well.

All patients with VPA TDM requested in year 2017 and fit the inclusion criteria were enrolled. All necessary information needed such as patient's demographic data, dosing information, sampling time, and others were acquired from the TDM request forms.

In our data, concentrations measured at steady state (Css) can be mostly regarded as average steady state concentrations. Therefore, the standard steady state clearance equation can be used to estimate the clearance of VPA, as follows (6):

$$\frac{\mathrm{CL(L/hour)}}{\mathrm{F}} = \frac{S \times Dose(mg)}{Css\ measured\ (mcg/ml) \times Interval\ (hour)}$$

Where CL = clearance

Css = steady state concentration

S = salt factor

F = bioavailability

For research purpose, it was assumed that the oral bioavailability and salt factor of VPA in oral solution and tablet is 1.0 whereas that of sustained release tablet was 0.9. CL/F can be calculated using the above equation.

The data were analysed using Statistical Package for Social Science (SPSS). Continuous data were analysed using independent *t* tests if the assumptions of normality are met; *p* value of less than 0.05 will be considered as statistically significant. The population VPA clearance was determined by calculating the mean. Correlation was measured by Pearson correlation test to analyse the age, weight and gender .

As this study only involved an analysis of patients' VPA pharmacokinetic profile and no direct patient contact, no informed consent form and participant information sheet was required. Approval from the Head of Department of the Pharmacy directorate for access of patient's medical record was given. The research was registered with the National Medical Research Register

(NMRR) and ethical approval from the Medical Research and Ethics Committee (MREC), Ministry of Health, Malaysia (NMRR-18-2578-43732).

For this research, the name and other identifiable documentations (e.g., identification card number) of the participants were not required. The only personal data of patients to be recorded were their age, gender, and ethnicity, which were not sufficient to identify any particular patient. Treatment wise, data recorded were diagnosis, concurrent medications, duration of treatment, dosage, creatinine, creatinine clearance, TDM level, elimination rate, and half-life. All medical records were reviewed in the Pharmacy Department itself and not taken out to further protect patient's privacy and confidentiality.

RESULTS

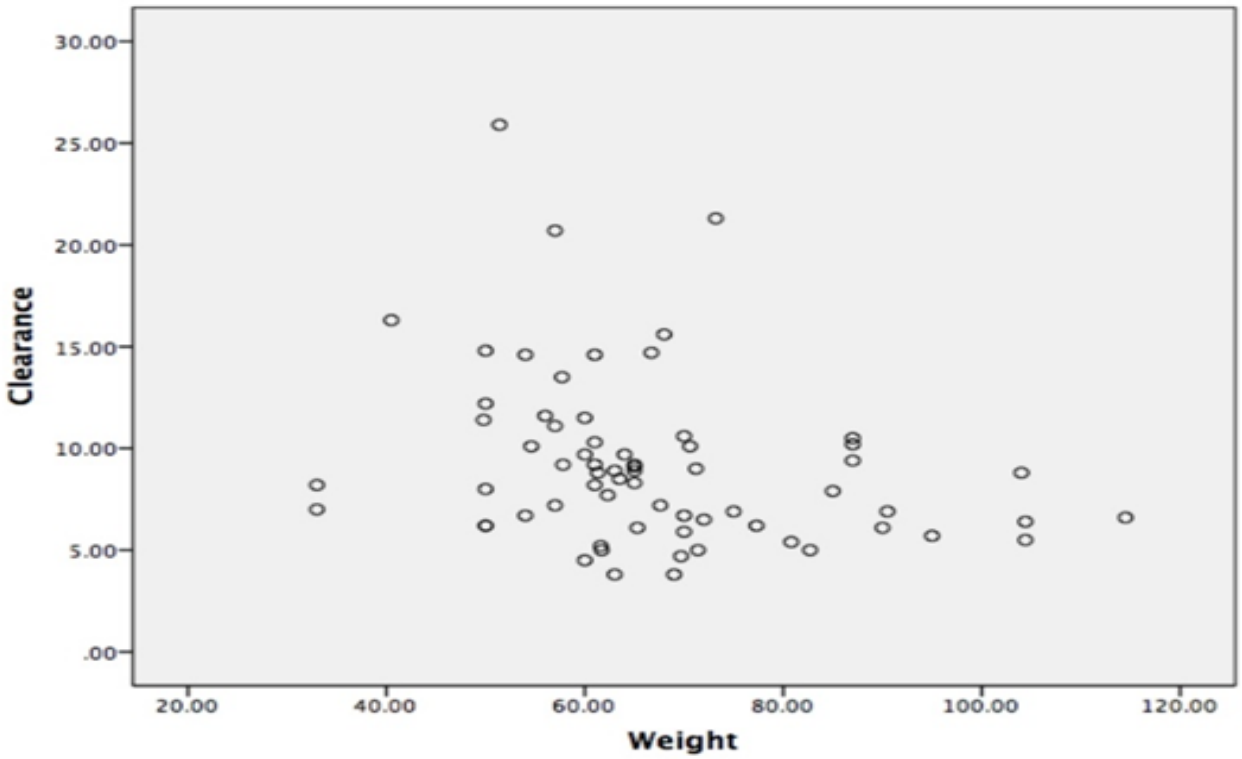
A total of 215 TDM request forms were derived from the year 2017. Only 67 samples were able to be analysed with 148 samples omitted based on the exclusion criteria. Calculated population clearance was 9.2ml/kg/hr (SD 4.19), which is within the estimated patient clearance range used for dose initiation. Characteristics of the study population are summarized in Table 1.

Table 1: Characteristics of the study population

Characteristics	Mean	SD	Frequency(Percentage)
Age (years)	41.1	14.86	
Weight (kg)	67.0	16.10	
Male/female			46 (68.0%) / 21(32.0%)
VPA dose (mg)	1037.0	395.75	

No positive correlation was found between VPA mean clearance and patient's age (r=0.02. p=0.89). An independent sample t-test also noted that there is no difference in VPA clearance between gender (p=0.27). A negative but weak correlation was however found between the weight and mean clearance (r =-0.29, p=0.02). No positive correlation was found between the dose and mean clearance (r=0.32, p=0.07). The scatter plot of the correlation is illustrated in Figure 1.

Figure 1: Scatter plot on correlation between weight and clearance



DISCUSSION

The primary aim of the study was to investigate the clearance of valproic acid in patients with mania associated with bipolar disorders in Sarawak General Hospital and Sentosa Hospital. The mean calculated population clearance was 9.2ml/kg/hr (SD 4.19). This value was in the range of the estimated value used for patient clearance which is often based on 7-12ml/kg/hr for monotherapy in adults (5).

As VPA pharmacokinetic (PK) profile may be affected by various factors including VPA dose, patients background, possible drug-drug interaction and changes in protein binding profile, the drug has a high PK variability between patients (4). Our study analysed the influence of body weight (kg), age (year) and gender on VPA CL/F. The results indicated that VPA CL/F was not affected by the patient's age and gender. However, a statistically weak negative correlation found was found between weight (kg) and VPA clearance.

The effect of age on VPA clearance has been studied widely. However, correlation was inconclusive. Our finding was consistent with the previous findings of Mohammadpour et al., Aghebati et al., and Birnbaum et al where no correlation were found, but was in contrast to the

findings of Battino et al. study and Yukawa et al. which found otherwise (6,7,8,12,13). No correlation between gender differences in Cl/F concurred with findings of other studies (13). However, a population study by Birnbaum et al. did showed that the clearance in female patients appeared to be roughly less than their male counterparts. Elderly home resident's CL/F was around 27.0% lower in females (8).

VPA drug is highly protein bound with low hepatic extraction ratio, with the former characteristics resulted in the nonlinear pharmacokinetics profiles of the drug. Thus, VPA concentration in the blood will rise exponentially once the relevant protein binding sites are saturated (4,14). The clearance of VPA correlates with the unbound concentration of the drug, with VPA being primarily eliminated by means of hepatic metabolism of the unbound fraction of the drug (9). Therefore, in relation to using high dose of VPA, the CL/F is predicted to be dependent on the prescribed daily dose. These outcomes further amplify the agreement with other related studies determining the effect of VPA dosing on CL/F. This study was done among patients in Sarawak General Hospital and Sentosa Hospital who received a variety of VPA doses based on the severity of their disorder and prescribers' clinical judgement (mean=1037mg/day). Even though the doses prescribed were relatively high in nature according to the mean value, there was no correlation between the VPA dose and clearance. The result correlates with the Bondareva study which revealed no relationship between the VPA dose and CL/F resulted from the saturation of its protein binding (14).

This only significant finding found in this study was a negative weak correlation (r=-0.29) of the patient's body weight (kg) to the VPA clearance (p=0.02). In contrast, the study done by Mohammadpour AH and the psychiatric and neurologic clinics of Ebn –sina and Ghaem Hospitals in Mashhad University of Medical Science in Iran, showed that the clearance of VPA was not affected by total body weight (6,7). Methaneethorn J reported that the clearance of VPA could be predicted from body weight of the patients, suggesting the association between weight and organ functionality and development for VPA clearance (12). Another PK model developed by Jankovic and Milovanovic has also demonstrated the clearance of VPA increased linearly with the total body weight. A larger sample size study might be needed to verify the correlation with weight.

CONCLUSION

The mean clearance (Cl/F) based on the study done was found to be 9.20ml/kg/hr (SD 4.19). Our study showed that there was no significant mean difference in mean clearance between male and female. There was no positive correlation of the mean clearance with the age and VPA dose with a weak negative correlation to weight. Nevertheless, for detailed result and interpretation of result and formation of VPA PK model in Malaysian patients, localised population clearance values enable a more precise dose recommendation for patients on VPA therapy for mania associated with bipolar disorder. A statewide study on VPA pharmacokinetic profile in this patient population is recommended to further validate the clearance value, enabling optimal dosing of VPA during initiation of treatment.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests to disclose.

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