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The Clinical Important Corrected Plasma Concentration During Valproic Acid Therapy for Thrombocytopenia in Patients with Hypoalbuminemia : A Case Report and Narrative Review

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ABSTRACT

Valproic acid (VPA) induced thrombocytopenia is associated with concentrationrelated side effects that is more prominent at higher VPA plasma concentration. Furthermore, in patients with marked hypoalbuminemia, there is a highly free and total concentration of valproic acid. However, there are limitations of measuring the free VPA concentration, which may require an algorithm for correcting total VPA concentration based on albumin level. We present a case of an 82-year-old female who received a 2.4-gram of VPA for post stroke seizure therapy. Despite VPA serum concentrations of 55.26 µg/mL, three days later the patient developed thrombocytopenia (platelets; 86 x10^3/µL). Therefore, we would propose a formula for correcting total VPA serum concentration based on albumin, she has been elevated of total normalized VPA plasma concentrations. Moreover, Bayesian dose-optimizing software was applied to estimate pharmacokinetic parameter in this patient, half-life 5.69 hr, clearance 1.32 L/hr and time to steady-state 22.78 hr. Consequently, the patient was decreased dosage of VPA to 1.8 g/day and her subsequent platelet was returned to 161 x10^3/µL in twelve days. In conclusion, it would be prudent to assess free fractions of VPA or use free VPA concentration for therapeutic monitoring in patients with a clinically significant hypoalbuminemia

Key words: Valproic acid, Plasma concentration, Thrombocytopenia, Hypoalbuminemia

Introduction

Valproic acid (VPA) is usually prescribed as an antiepileptic drug indication for seizure from any causes. The unique of VPA pharmacokinetic characteristics is extensive bound 90% to plasma protein (bound VPA concentration), preferential albumin. If the hypoalbuminemia was marked, the albumin concentrations were less than 2.5 g/dl[1]. Once the VPA concentrations were achieved to the steady-state consequenc-

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es, and there was a resulting in an increase of the unbound VPA concentration. Even though the bound VPA plasma concentrations may be in either a sub-therapeutic or in the therapeutic range due to the pseudo-linear pharmacokinetic. This error might cause a misleading into the interpretation in the clinical practice, the clinicians may increase dosage of VPA that would promote VPA toxicity, thereby the concentration-related adverse effects are frequently occurred[2]. Valproic acid induced thrombocytopenia (VIT) is associated with dose and concentration dependent[2], which is an unrequired state that can be encountered in practice, but most cases were ignored by the clinicians. The prevalence rate of VIT was 12-18%[2, 3]. Additionally, the patient had multiple risk factors such as, duration of the exposure of VPA, women who are sexually exposed are more likely than men to develop VIT[2]. Some studies report that the older adults are more likely to develop VIT[2].

Currently, there is no accurate equation used to predict VPA plasma level, especially in patients with hypoalbuminemia. We describe a case report and review the literatures, the patient diagnosed post stroke seizure having a hypoalbuminemia and thrombocytopenia due to VPA during sub-therapeutic or in therapeutic range of bound VPA plasma concentration. The purpose of case study discussion is to describe in the setting that limited to measure the unbound VPA plasma concentrations in the patient having marked hypoalbuminemia may predict VPA plasma level by use total normalized VPA plasma concentrations formula. After correction of plasma albumin concentrations and VPA dosage adjustment based on monitoring platelet count and total normalized VPA plasma concentrations[4], the patient's platelet count was turned to a normal range.

Report of a case

An eighty two years old female who had having a weakness in her right leg and right arm was admitted to a provincial hospital before she was diagnosed as having the acute ischemic stroke (AIS). According to her past medical history, she also had been diagnosed with an atrial fibrillation, hypertension, diabetes mellitus type 2, hyperlipidemia, chronic kidney disease (CKD) stage 4 and asthma. This patient had none of drug allergy history and denied to take supplementary food and herbs. The patient was firstly diagnosed to have an acute ischemic stroke (AIS) at a provincial hospital and was later transferred to the hospital medical college. Her latest physical examination was resulted that: Glass glow coma score (GCS) E3V1M5, spontaneous eye opening, motor left grade 3 all/right grade 0 all, NIHSS score was 20, finally the thrombectomy was not performed because the ASPECT score was less than 6 points.

Additionally, due to a post stroke seizure, the patient was assessed by electroencephalography (EEG). The result indicated that the patient's brain showed epileptic foci (ictal discharge from left hemisphere with secondary generalized) and she was basically given levetiracetam 1,000 mg Intravenous (IV) every 12 h (2,000 mg/day) and diazepam 10 mg IV immediately. After that, the patient was hospitalized in the hospital medical college at the acute stroke unit. The medication during admission in the hospital as follows: warfarin 17.5 mg total weekly

dose, manidipine 20 mg/day, carvedilol 18.75 mg/day, enalapril 5 mg/day, levetiracetam (LEV) syrup (100 mg/ml) 10 ml every 12 h (2,000 mg/day), lacosamide (LCM) 100 mg every 12 h (200 mg/day), rosuvastatin 10 mg/day, fluticasone propionate/salmeterol (250/25 µg) evohaler 2 puff twice daily, ipratropium bromide/fenoterol hydrobromide (0.02/0.05 mg) MDI 2 puff every 6 h, montelukast 10 mg/day, omeprazole 20 mg/day before breakfast 30 minute, vitamin D2 (20,000 IU) 1 capsule 3 times/week and calcium carbonate 1,500 mg/day. The patient's albumin concentration baseline was significantly lower (2.08 g/dl) than normal range (2.6-5.2 g/dl), and the other laboratory baseline as follows: hemoglobin (Hb) 9.1 (12-16 g/dl), hematocrit (Hct) 30.3 (37-47%), serum creatinine (S.Cr) 1.05 (0.5-1.2 mg/dl), blood urea nitrogen (BUN) 43 (6-20 mg/dl), INR 2.5 (2-3), total bilirubin (T.b.) 0.26 (0-1 mg/dl), direct bilirubin (D.b.) 0.19 (0-0.4 mg/dl), aspartate aminotransferase (AST) 14 (0-37 U/L) and alanine aminotransferase (ALT) 8.5 (0-40 U/L).

After the patient was given VPA 1,200 mg/day combination with LEV and LCM as above (day 1) and then six days later her platelet count had been decreased from 242 to 135 x 10^3 /µL Fig.1 (Phase I). After 17 days later she had tonic seizure on her right arm and VPA was increased up to 1,800 mg/day and day 23 her physical examination was indicated nystagmus positive. We assessed that the total VPA trough concentration was observed only 25.38 µg/ml. The patient's albumin concentration was observed only 0.95 g/dl. The platelet count is nearly about 133-137 x10^3/µL (Phase II). Due to the total VPA trough concentrations was lower than the therapeutic range (50 – 100 µg/ml). The VPA dose increased about 33% (2,400 mg/day). Notably, the patient's platelet count was decreased from 133 to 86 x 10^3 /µL. White the total VPA trough concentrations and albumin concentration were observed 55.26 µg/ml, 2.29 g/dl respectively (Phase III).

Consequently, she was diagnosed thrombocytopenia and the hematologist was consulted to assess to rule out other hematological diseases, at this point the patient was more investigated e.g. platelet blood smear (PBS) test by hematologist and the next day hematologist suspected VIT. The neurologist was consulted to assess antiepileptic drug dosage, regardless the patient had had the thrombocytopenia, the patient was recommended to decrease the VPA dose to 1,800 mg/day. Meanwhile the liver function was resulting in a normal and the total VPA trough concentration and albumin concentration was observed 40.14 µg/ml, 2.12 g/dl respectively (Phase IV). Regarding to VIT the patient did not have the clinical signs of bleeding, therefore there is not an indication for platelet transfusion[5].

Since reducing the dose of VPA, topiramate 100 mg/day was added to control the seizures and the patient did not have any seizure symptoms or an absence of epileptiform, discharged on the EEG another day. After day 30 the patient's platelet count was obtained again, it increased nearly at baseline within 12 days (161 x10^3/µL). However, the Bayesian dose optimizing software was performed to estimate the individualized pharmacokinetic parameters as follows (Fig. 2); half-life 5.69 hr, clearance (CL) 1.32 L/hr, volume of distribution (Vd) 10.85 L and time to steady-state (TSS) 22.78 hr.

Figure 1 Timeline relationship of the patien's platelet count, VPA level and VPA dose

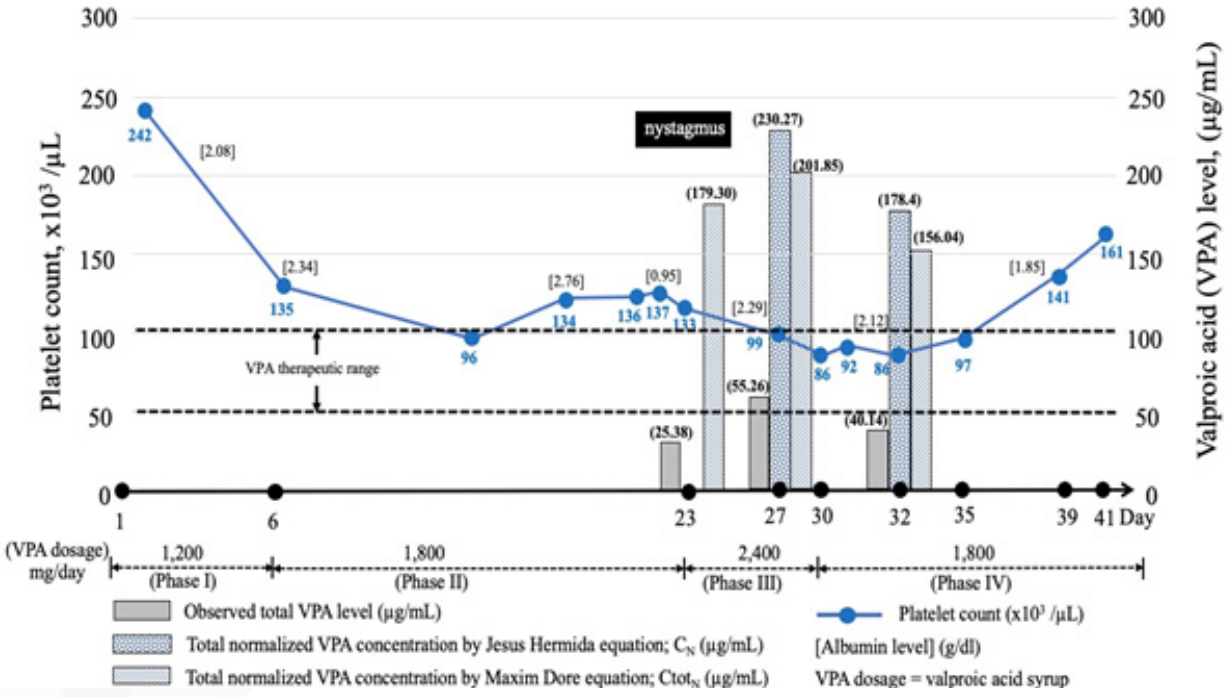
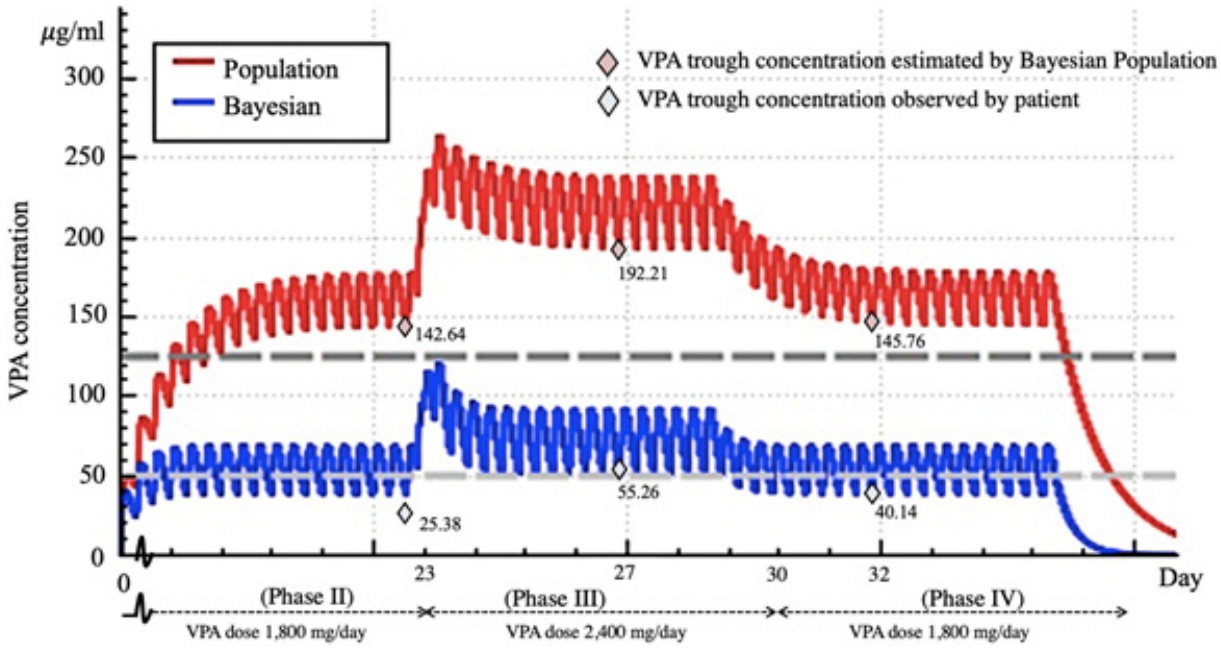


Figure 2 Relationship between VPA concentration and time to observed VPA trough concentration by the Bayesian Pharmacokinetic Parameter



Discussion

Based on the VPA pharmacokinetics at the therapeutic concentrations, it's able to bind 90% of plasma albumin[6] to become a "bound VPA", so there are free VPA in the plasma called "unbound VPA". Due to the VPA is capacity-limited binding sensitive[7] and the unbound VPA is only eliminated almost completely via hepatic metabolism. Therefore, changes in the plasma albumin concentration and the binding characteristics can significantly alter their hepatic clearance. In addition, the VPA is a low hepatic extraction ratio when the dose or the concentration of VPA was increased, the clearance (CL) rate was increased simultaneously, while the unbound VPA plasma concentration fraction increased in a proportional fashion in a linear. Even though the bound VPA plasma concentrations may be in either a sub-therapeutic or in the therapeutic range, it could be primarily assumed that the unbound VPA plasma concentrations may actually be increased or over the therapeutic range. Thus the measurement of the "unbound VPA" plasma concentrations should be considered in patients with the altered VPA plasma protein binding such as hypoalbuminemia[8]. In addition, the patient whose comorbid disease was CKD Stage 4 could be increased BUN so that they will be displaced to albumin instead of VPA promoting the higher unbound VPA plasma concentrations and increased the VPA side effect[8].

Thrombocytopenia is defined as a platelet count of less than 150 $x10^3/\mu L$[9]. The VPA induced thrombocytopenia (VIT) happened when the drug caused cytotoxic myelosuppression and it is a concentration dependent mechanism[1]. It took an average of 82 days (range 38-170 days) to develop VIT[1] and some study suggested that at least 3 days to 16 months[10, 11]. Its prevalence rate was 12-18%[2, 3]. In this regard, the previous studies had been identically suggested that the patients had several risk factors associated with VIT e.g. having a low initial platelet count, being female, being elderly, using VPA more than 1 g/day, and having more than 100 µg/ml of VPA concentration (VPA concentration dependent)[2, 12, 13]. As a consequence, this patient firmly had several risk factors associated with VIT including: 1) having a low platelet count as initially found in Phase I and II; 2) being female gender; 3) 82 years old; 4) having been using VPA dose over 1-g/day; 5) having been given VPA for 30 days and 6) having the predict highly of total normalized VPA concentration by Jesus Hermida equation (C_N) and total normalized VPA concentration by Maxim Dore equation (CtotN) which is supra-therapeutic range.

In clinical practice, there is a few of laboratory that is able to measure with the unbound VPA plasma concentrations. It is necessary to review a literature with an equation that is able to predict VPA concentrations in the patient who have a hypoalbuminemia. According to finding of two studies, the equations had been proposed to predict the total normalized VPA concentrations in the patient having hypoalbuminemia. First, based on the study of Jesus Hermida and J. Carlos Tutor[4], the predict C_N was performed by the indirect method (Fig.1). However, the predict C_N (Phase I) was not performed because the patient's albumin was more extremely lower (0.95 g/dl). According to Jesus Hermida's equation, it defined the lowest of incremental changes in

serum albumin concentration correlated with free fraction (∂) of VPA is 1.8 g/dl. The second study, Maxim Dore et, al[14], an equation in this study was proposed to estimate the CtotN by the direct method, the predict CtotN was performed (Fig.1).

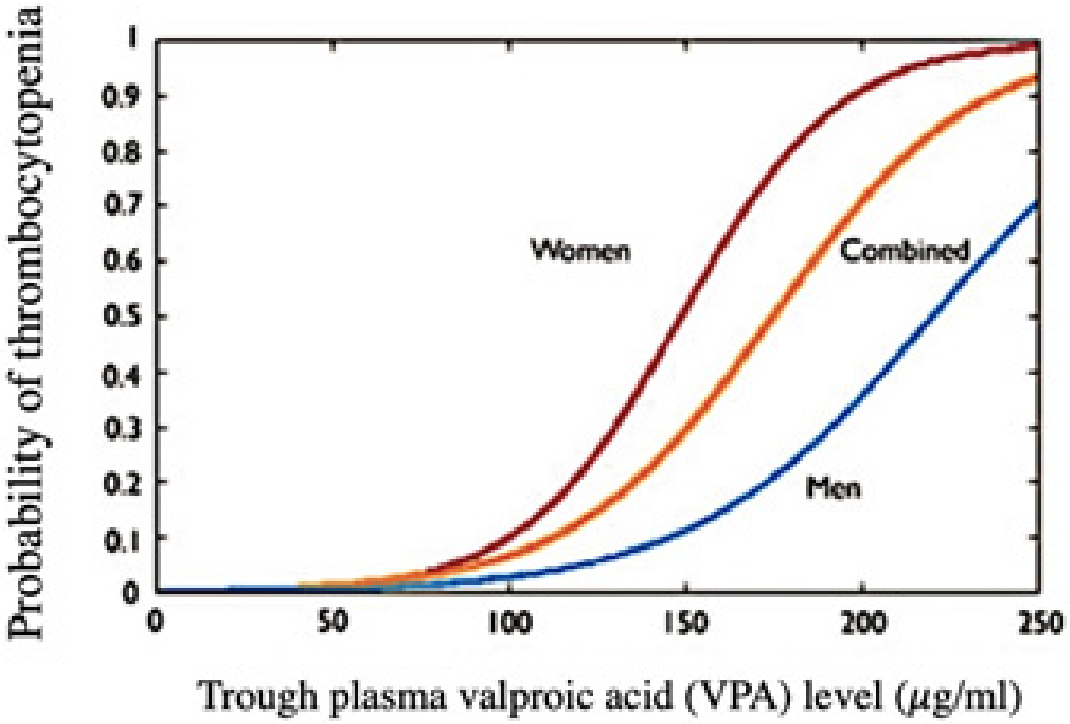
According to a clinical application, the external validity may be more considered in detail. The patients were included to participate in the study by Jesus Hermida et al, they were different from this patient in some issues such as their albumin concentrations were higher (range 2.4 - 4.1 g/dl), they were younger (25-55 years old), they also took other anticonvulsants (30.18%) e.g. phenytoin, carbamazepine, and lamotrigine and almost the participant patients were not identifiable to be inpatients or outpatients. As well as Maxim Dore study, the patient's albumin concentrations were higher (range 2.3 – 3.5 g/dl) except their ages were 27-85 years old and all of the participant were identified to hospitalize or follow as outpatients, thereby the factor that is comparable in this context is an age and those hospitalized patients. Almost both of these studies the patients had a normal bilirubin, serum creatinine, and blood urea nitrogen, which were different from this patient who suffered from CKD stage 4 with higher bun. By the way, she has an advanced age (82 years old) and she had an albumin concentration almost lower than 2.3 g/dl (marked hypoalbuminemia). These risk factors are the limitations for using the equations to predicted VPA levels may be inaccurate and misinterpretation that could lead to an overestimation of the normalized concentration of VPA. It may significantly influence the efficacy or the toxicity because VPA is a drug with narrow therapeutic index.

However, the only thing that patient had the marked hypoalbuminemia according to the Maxim Dore's equation may be more available option because this is the direct estimation method to predict both of CtotN and Cu. Consequently this effected to C_N higher than CtotN about fourteen percent (Phase III, IV). Thus it's could presumable that the value of CtotN and Cu may be more reliable than C_N. Because the Jesus Hermida's equation giving the incremental changes in serum albumin concentration correlated base on the free fraction (∂) of VPA, which the alpha (∂) is bring to multiply in an equation instead. Therefore the albumin concentrations are likely to be the indirect variable to estimate C_N. Meanwhile, the Maxim Dore's equation giving the actual patient's albumin concentrations to be a direct cofactor to multiply with other variables. Moreover, the recent study supporting was found that there was a discordance between the predicted (C_N) and measured unbound plasma VPA concentrations when using the Jesus Hermida's equation, due to the potential impact of overestimation, because they had an extraordinary found that the metabolic abnormalities might be marked the severity of illness rather than influencing the isolated albumin[15].

The Bayesian dose optimizing software is a precise program, it has been widely used to analyze pharmacokinetic parameters that is able to analyze the sparse individual data, which has the advantages over using the prediction equations. The principle is to create a pharmacokinetic model that takes into account for various factors in patients, such as age, weight, various

medications used together and other factors that affects the pharmacokinetic parameters due to the effects of an interindividual variability[16, 17]. Bayesian software was performed to confirm the precision of the Maxim Dore's equation in Phase III and IV. The VPA trough concentrations estimated of the population by Bayesian software are comparable with the CtotN by using the Maxim Dore's equation, 192.21 µg/ml and 145.76 µg/ml by the Bayesian software (Fig.2), 201.85 µg/ml and 156.04 µg/ml by the Maxim Dore's equation (Fig.1), respectively. Remarkably, in Phase III the VPA trough concentrations (179.30 µg/ml), by the Maxim Dore's equation, were more elevated than the estimated of the population (142.64 µg/ml). Because in day 23 the patient's albumin concentrations (0.95 g/dl) had more extremely lower than the participated patients in the Maxim Dore study which effected to overestimate the VPA trough concentration (179.30 µg/ml).

Figure 3 Probability of developing thrombocytopenia at various trough plasma VPA levels[1]



Finally, due to a considering patient's platelet count, the neurologist decreased the VPA dose to 1,800 mg/day. However, it will be the same dose as before the thrombocytopenia. Based on data from the previous report suggested that the level of VPA plasma concentration (concentration response) to be more predictive of thrombocytopenia than using the dose of VPA (dose response) because it may come from the effect of the interindividual variability such as age, weight, absorption and drug elimination rate that is different for each person[18]. Moreover, previous case report which found that the probability of the thrombocytopenia associated with the VPA plasma trough concentration in both males and females (Fig.3)[1]. However, in that study, the platelet levels in all subjects could returned to baseline by reducing the dose or discontinue VPA[1]. Therefore, in this patient's, the neurologist reduced the VPA dose to the lowest possible to maintain the treatment efficacy and closely monitored the patient's VPA plasma and platelet level. According to the individualized pharmacokinetic parameter from Bayesian dose optimizing software the new steady-state achieved within one day (TSS 22.78 hr), the total VPA trough concentration was decreased from 192.21 µg/ml to 145.76 µg/ml. The platelet count was increased again up to 161 $x10^3$/µL within 12 days consistently as the previous case report that the platelet had increased within 1–3 weeks[19].

Conclusion

If it were required to accurate therapeutic VPA monitoring for the elderly patients with marked hypoalbuminemia and various comorbidities, however, the authors recommended that the VPA level should be measured from the unbound VPA plasma concentrations (free drug). If the laboratory setting unavailable, the Maxim Dore's equation may be more interesting than Jesus Hermida's equation to correct the normalized total VPA plasma concentrations. In this case, VIT can be solved by decreasing the VPA dose and close monitoring platelet concentration before and during period of VPA exposure.

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