

Therapeutic drug monitoring of valproic acid

Abdul Sami Shaikh^{1,2}, Huanjun Liu¹, Yi Li³, Lili Cao³ and Ruichen Guo^{1*}

¹Institute of Clinical Pharmacology, Qilu Hospital of Shandong University, Jinan, China

²Department of Pharmacy, Shah Abdul Latif University, Khairpur, Pakistan

³Department of Neurology, Qilu Hospital of Shandong University, Jinan, China

Abstract: The unpredictable and unfavorable connection of dose and plasma concentration of valproic acid supports the necessity to regularly measure its plasma concentration. The present study is drug monitoring of valproic acid and comparative evaluation of therapeutic monitoring results of valproic acid for assessment of clinical response, safety and toxicity in different age and gender groups of Chinese epileptic patients. This knowledge will help the clinicians in adjusting the drug dosages of valproic acid in various sub-groups of epileptic patients for enhancing the safety and minimizing the toxicity of valproic acid. A total of 206 plasma samples (126 males and 80 females) of epileptic patients using valproic acid were requested for therapeutic drug monitoring by neurology department of Qilu Hospital. It was found that 29 % of the total samples were found in sub-therapeutic levels, 13% of the samples had toxic levels and 58% of all the samples had valproic acid levels in therapeutic range. The difference in plasma concentration of valproic acid is notably altered in gender and various age groups. However, this requires further investigation. Despite the majority of samples in the therapeutic range, there was an unfavorable clinical response. The outcomes of the current research work exposed that there was a poor correlation between the plasma concentration and clinical response. Careful attention must be applied to specific gender and particular age group on an individual basis in the interpretation of plasma concentration results, in order to facilitate the modification of doses and develop the best approach in treatment and to obtain the desired clinical response because multiple factors can affect the valproic acid plasma concentration. Through these results, it can be concluded that poor correlation exists between valproic acid plasma concentration and clinical response.

Keywords: Therapeutic drug monitoring, Valproic acid, Valproate.

INTRODUCTION

Valproic acid or Valproate (VPA) is from the most commonly prescribed antiepileptic drugs. Drug monitoring can provide a critical commitment in epilepsy field and antiepileptics. The determination and analysis of plasma or serum drug concentrations (SDC) may be useful in treating irrepressible seizures and adverse effects. Therapeutic Drug Monitoring (TDM) can help in the individualizing of treatment and in modifying for unpredictable pharmacokinetics; and it is valuable in unique populaces, for example, pregnancy (Jacob and Nair, 2016). SDC is mainly applicable in the pediatric and psychiatric problem sufferers requiring difficult clinical evaluation. It is additionally helpful for dose modification in complex epilepsy that may require numerous drug therapies (Jacob and Nair, 2016). Both physicians and pharmacologists have for some time been occupied with finding out why a similar drug dose is viable in only a few patients. A few years ago, the adequate and desired dosage was brought about by trial and error. With the emergence of knowledge of measuring plasma concentration in biological fluids, it has enabled us to examine the association between dosage of drugs, plasma concentration in biological fluids and systemic actions and as a result, deliver new understandings into drug therapy. It has been noted generally within a reference

range of plasma concentrations, the therapeutic effect of most of the antiepileptic drugs accomplished; while too low concentrations are more probably to produce an inadequate effect, on other hand, too high plasma concentrations are commonly related with serious side effects. TDM is recommended for a number of antiepileptics including valproic acid and usually used as a very important tool for individual patients for selecting the optimum therapy regimens. This attitude further facilitates and helps the physicians in knowing why some patients do not respond reasonably to a specific dosage. Additionally, Therapeutic drug monitoring help us to evaluate non-compliance, besides that variation in pharmacokinetics which arises among and between the individuals and the elements accountable for these type of variation can be examined (Patsalos *et al.*, 2008) Generally speaking, maximum sufferers of epilepsy are ideally managed with valproate serum concentration of 50–100ug/mL (Neels *et al.*, 2004). The antiepileptic's pharmacokinetics is noticeably impacted by age, particularly amid earliest stages and childhood (Hadjiloizou and Bourgeois, 2007). A case report regarding the toxicity of valproic acid in a child has been reported recently. A child of age- 23 months, who was initially quarantined with onychomadesis, had a problem related to valproate therapy and the family was nervous but it was spontaneously fixed. The improvement of this very rare adverse effect of antiepileptic drugs after cessation of valproic acid without treatment is

*Corresponding author: e-mail: grc7636@126.com

emphasized (Güler *et al.*, 2017). For most AEDs contemplated in infancy and childhood, pharmacokinetic qualities incorporate shorter disposal half-lives and, on occasion larger volume of distribution values in grown-ups. Due to their higher leeway, newborn children may need a dose that might be twice or thrice more than that need to accomplish a similar medication focus in a grown-up. Clearance values diminish slowly all through childhood, yet the exact time course of this procedure isn't entrenched and is portrayed by an articulated interindividual fluctuation (Perucca, 2006). Due to quickly changing clearance, it is extremely hard to manage babies with antiepileptics without observing plasma concentrations of drugs. Steady-state plasma drug concentrations do not specifically occur in infants due to their pharmacokinetics being altered upon reaching steady-state (Bourgeois and Dodson, 1983). The present study is therapeutic drug monitoring of valproic acid in patients having persistent seizures or patients suspects of adverse effects or overdose, and comparative evaluation of therapeutic monitoring results of valproic acid for assessment of their possible relationship with clinical response, safety and toxicity in different age and gender groups of Chinese epileptic patients.

MATERIALS AND METHODS

The present study is directed towards evaluating and comparing the plasma levels of VPA in Chinese epileptic patients obtained with Enzyme-multiplied immunoassay technique (EMIT) for assessment of clinical response, safety and toxicity in different age and gender groups. Therapeutic drug monitoring data of VPA obtained with EMIT in our laboratory was compiled and evaluated by a registered pharmacist using statistical software of SPSS. Valproic acid TDM results of total 206 epileptic patients were compiled, evaluated and compared for compliance, safety and toxicity in different age and gender groups of Chinese epileptic patients. The results were further characterized as per plasma concentrations levels of VPA into (Sub therapeutic range, therapeutic range and toxic range). All patients were divided into two separate gender groups; males and females, and then each gender group was further subdivided into infants, children, adult and elderly patients as different age group. The samples of male patients were (126) and samples of female patients were (80).

RESULTS

Therapeutic drug monitoring results of valproic acid revealed that 58% of Chinese patients taking valproic acid had the drug in therapeutic levels. The plasma VPA levels were found in sub-therapeutic level in 29% of patients and 13% patients had found in toxic levels. The females had 36 % samples in sub-therapeutic levels while males had 25 % samples in sub-therapeutic levels. As compared

to adults and elderly patients (both males and females); children (males) and infants (females) had an increased number of samples within sub-therapeutic levels.

DISCUSSION

The samples of valproic acid users of 206 epileptic patients have been received and analyzed successfully for therapeutic drug monitoring of valproic acid in Chinese epileptic patients. TDM results of VPA have been evaluated and compared for assessment of clinical response, compliance, safety and toxicity in different age and gender groups of Chinese epileptic patients. Our results of therapeutic levels were agreed with with Shakya *et al* (Shakya *et al.*, 2008) who reported 62% patients had concentration levels of VPA in therapeutic levels. Shakya *et al* reported that 20% and 18% samples were in sub-therapeutic and toxic ranges respectively. One of the major reasons for more samples in sub-therapeutic concentration levels of VPA possibly could be due to non-compliance of patients. One of the ways of improving the compliance properly can be restricting these patients to take a limited number of appropriate daily doses and besides that, all patients' especially non-compliant patients should be regularly monitored for VPA plasma concentrations to ensure that these patients are observing full compliance. Our major reason behind the increased number of sub-therapeutic samples in females or having low concentration could be due to poor compliance, underdose, improper dose and co-medication of enzyme-inducing drugs. Reports suggest an increase in an unbound fraction of valproic acid in late pregnancy, in elder patients, patients suffering renal diseases, chronic liver disease and conditions linked with decreased albumin count (Patsalos *et al.*, 2008). No noteworthy changes are observed in unbound concentrations of valproic acid despite a significant reduction of 50% or even more in overall concentrations (Koerner *et al.*, 1989; Yerby *et al.*, 1992) for profoundly protein-bound drugs. For example, total plasma concentration of valproate and phenytoin might misdirect amid pregnancy, understating the pharmacological impacts of the drugs. A reduction in protein binding in essence will bring about lower total (protein bound in addition to unbound) drug concentration, yet may leave unaltered the unbound, pharmacologically active concentration of the medication. Children (males) and infants (females) had an increased number of samples within sub-therapeutic levels. This may be due to rapid metabolism in infants and children or also may be due to non-compliance or insufficient dose. In a populace of infants and children, it has been recommended that effective dose of valproate may not be accomplished despite of higher dosage than 100 mg/kg/day in a large number of patients co-medicated with enzyme invoking Antiepileptics. It is also reported that children need greater dosages to accomplish plasma VPA concentrations equivalent to those witnessed in

Table 1: TDM results of Valproic acid in all patients according to age groups

Groups	Therapeutic Range N (%)		Sub-therapeutic Range N (%)		Toxic Range N (%)		Total no of samples	
	Males	Females	Males	Females	Males	Females	Males	Females
Infants	6 (54)	5 (42)	2 (18)	7 (58)	3 (28)	0	11	12
Children	43 (58)	28 (55)	20 (27)	14 (27)	11 (15)	9 (18)	74	51
Adults	28 (74)	7 (44)	7 (18)	8 (50)	3 (8)	1 (6)	38	16
Elderly	1 (33)	1 (100)	2 (67)	0	0	0	3	1
Total	78 (62)	41 (51)	31 (25)	29 (36)	17 (13)	10 (13)	126	80

adults (Cloyd *et al.*, 1993). The concentration results of VPA in all patients including males and females according to age groups are presented in table 1.

Quantifying plasma concentrations are very helpful. A low measurement reveals either poor recent compliance or undertreatment. Poor compliance is suspected when recommended dose to the patient is not related to measured low concentration or earlier concentration levels guide that the plasma concentration levels should be greater for the certain dose (Kang and Lee, 2009). The present results suggested that there is a different metabolic pattern in different gender and age groups.

TDM results showed that a sufficient number of samples were in sub-therapeutic and toxic levels. The increased numbers of female samples were in sub-therapeutic levels in comparison to males. In males, children samples were more in sub-therapeutic range as compared to infants, adults and the elderly. Infant female samples were more in sub-therapeutic range as compared to children, adults and the elderly. However, sub-therapeutic levels may be not enough to control seizures adequately. An increased number of female, male children and female infant samples within sub-therapeutic range may be due to non-compliance or improper dosages which results in an unfavorable clinical response. In the gender group: Female and in the age groups: Children (Male) and Infant (Female) may require a higher dosage to achieve the desired clinical response. The findings of this study are extremely useful and suggest that further investigations are required especially in patients with an insufficient seizure control and if patients are taking an appropriate dose with proper compliance, then all patients with low concentration levels may require more dosage, especially in infants and children due to rapid metabolism of VPA. Male and females samples were in equal proportion in the toxic range. The infant males were more in the toxic-range as compared to children, adults and the elderly males; while children females were more in the therapeutic range as compared to the infant, adult and elderly females. However; further evaluation is required. The association between dosage and resulting plasma concentration relies on pharmacokinetic changeability.

Main bases of pharmacokinetic changeability comprise lack of patient compliance, age (neonates, children, elderly), physiology (gender, pregnancy), drug-drug interactions and environmental influences. However, dose adjustments to maintain plasma drug concentrations within therapeutic range can greatly affect pharmacokinetic variability (Nwobodo, 2014). Therefore, routine monitoring of serum concentrations of the antiepileptic drugs is extremely useful, particularly in children and in patients who require associated antiepileptic medication (Yukawa *et al.*, 2000). Long-term use of AEDs showed adverse effects on the undeveloped brain than compared to a developed brain (Bittigau *et al.*, 2003). It would be very useful if a threshold concentration is known in order to set a range for newborns & infants, to maintain upper limit in young infants because it is tough to determine clinical toxicity in them (Walson, 1994). TDM is also useful in order to assess the compliance, optimize the safety, efficacy and minimize the toxicity. The present findings are very helpful for neurologists and epileptic patients, especially in optimizing the daily dosages of VPA.

CONCLUSION

The findings of the present study revealed that the relationship between plasma concentration of valproic acid and clinical response is not substantial. Less than half of the patients were out of the therapeutic range but the rest were in therapeutic range, despite both groups having an unfavorable clinical response. The difference in plasma concentration of valproic acid is notably altered in gender and different age groups. However, it needs further evaluation. It is suggested that therapeutic drug monitoring of valproic acid should only be performed when there is a suspicion of toxicity or insufficient clinical response or where it is difficult to observe the response e.g. in pregnancy, polytherapy, age groups (children & elderly), pathological conditions.

ACKNOWLEDGEMENTS

This study was supported by Major National Science and Technology Project (2012ZX09303-016-003).

REFERENCES

- Bittigau P, Sifringer M and Ikonomidou C (2003). Antiepileptic drugs and apoptosis in the developing brain. *Ann. N. Y. Acad. Sci.*, **993**: 103-114.
- Bourgeois BF and Dodson WE (1983). Phenytoin elimination in newborns. *Neurology*, **33**: 173-178.
- Cloyd JC, Fischer JH, Kriel RL and Kraus DM (1993). Valproic acid pharmacokinetics in children. IV. Effects of age and antiepileptic drugs on protein binding and intrinsic clearance. *Clin. Pharmacol. Ther.*, **53**: 22-29.
- Güler S, Isık I and Iscan A (2017). Onychomadesis: A rare adverse effect in early-period valproic acid therapy. *Turkish Archives of Pediatrics/Türk Pediatri Arşivi*, **52**: 98-100.
- Hadjiloizou SM and Bourgeois BF (2007). Antiepileptic drug treatment in children. *Expert. Rev. Neurother.*, **7**: 179-193.
- Jacob S and Nair AB (2016). An Updated Overview on Therapeutic Drug Monitoring of Recent Antiepileptic Drugs. *Drugs in R&D.*, **16**: 303-316.
- Kang JS and Lee MH (2009). Overview of therapeutic drug monitoring. *Korean J. Intern. Med.*, **24**: 1-10.
- Koerner M, Yerby M, Friel P and McCormick K (1989). Valproic acid disposition and protein binding in pregnancy. *Ther Drug Monit.*, **11**: 228-230.
- Neels HM, Sierens AC, Naelaerts K, Scharpe SL, Hatfield GM and Lambert WE (2004). Therapeutic drug monitoring of old and newer anti-epileptic drugs. *Clin. Chem. Lab. Med.*, **42**: 1228-1255.
- Nwobodo N (2014). Therapeutic drug monitoring in a developing nation: A clinical guide. *JRSM Open*, **5**: 2054270414531121.
- Patsalos PN, Berry DJ, Bourgeois BF, Cloyd JC, Glauser TA, Johannessen SI, Leppik IE, Tomson T and Perucca E (2008). Antiepileptic drugs--best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. *Epilepsia.*, **49**: 1239-1276.
- Perucca E (2006). Clinical pharmacokinetics of new-generation antiepileptic drugs at the extremes of age. *Clin. Pharmacokinet.*, **45**: 351-363.
- Shakya G, Malla S, Shakya KN and Shrestha R (2008). Therapeutic drug monitoring of antiepileptic drugs. *JNMA. J. Nepal. Med. Assoc.*, **47**: 94-97.
- Walson PD (1994). Role of therapeutic drug monitoring (TDM) in pediatric anti-convulsant drug dosing. *Brain Dev.*, **16**: 23-26.
- Yerby MS, Friel PN and McCormick K (1992). Antiepileptic drug disposition during pregnancy. *Neurology*, **42**: 12-16.
- Yukawa E, Hokazono T, Satou M, Ohdo S, Higuchi S and Aoyama T (2000). Pharmacokinetic interactions among phenobarbital, carbamazepine and valproic acid in pediatric Japanese patients: Clinical considerations on steady-state serum concentration-dose ratios. *Am. J. Ther.*, **7**: 303-308.