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CASE REPORT OPEN ACCESS

Systematic Approach in Long Term Pharmacological Treatment of Epilepsy: A Case Report on the Use of Valproic Acid

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Abstract

This is a case of breakthrough seizure and use of valproic acid (VPA) in management. Objective is to discuss the systematic approach in pharmacological treatment of epilepsy. Day one, patient was initiated with intravenous infusion of phenytoin 800mg, tablet phenytoin 300mg OD and tablet VPA 400mg TDS. Tablet VPA doses were withheld at Day 2 after Therapeutic Drug Monitoring (TDM) toxic levels. Patient was discharged with tablet VPA 400mg BD and tablet levetiracetam 500mg BD. In the beginning of therapy, a single pharmacotherapeutic agent is introduced cautiously to reduce any unwanted incidences of idiosyncratic and dose related toxicity. The pharmaco therapeutic agent dose must then be increased gradually to a maximum tolerated drug-dose therapeutic response. If this agent is not tolerated, it can be substituted with another agent for efficacious mono therapy. If seizures prevail, despite adequate trials of two appropriate agents, then poly therapy should be initiated. Patients need to be informed about the objectives of therapy and the risks and benefits of treatment.

Key words: Valproic acid, Seizure, Epilepsy, Pharmacological treatment, Malaysia.

INTRODUCTION

The main treatment for epilepsy is using Anti-Epileptic Drugs (AEDs). The strategy to develop AEDs is based on the path physiologic understanding of the condition. This understanding is then used to develop AEDs with multiple Mechanisms of Action (MOA). Hence, AEDs can broadly be categorised into five categories based on its MOAs.[1] The first is Ion Channel Modulators (ICM). ICM functions by reducing neuronal excitability. The target molecule is either calcium ion channel (ethosuximide, gabapentin and pregabalin), potassium ion channel (retigabine) and sodium ion channel (carbamazepine, eslicarbazepine, lacosamide, lamotrigine, oxcarbazepine, phenytoin, rufinamide). The second is enhancers of GABAergic transmission. This agent acts via positive allosteric modulation of the GABA A receptor (benzodiazepines, phenobarbital), reuptake inhibition of GABA (tiagabine) and enzyme inhibition of GABA metabolism (vigabatrin). The third is modulators of presynaptic machinery. Levetiracetam, which interacts with the presynaptic protein Synaptic Vesicle glycoprotein 2A (SV2A). The fourth is selective postsynaptic inhibitors of excitatory neurotransmission. Perampanel, which is a selective inhibitor of postsynaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate-receptor activity. The fifth is compound with multiple mechanisms (felbamate, topiramate and valproate).

CASE REPORT

This is a case report of a 44 years old Malay man. His current AED medication was only tablet VPA 400mg TDS, daily dose of 1200mg (Daily dose of 30mg/kg/day). He was previously on tablet Phenytoin 300mg ON but it was stopped in May 2018. No clear indication on why it was de prescribed. Patient self-reported and claims to be medication compliant.

On 16th August 2018 at 2300H, patient was resting at home with family members. He then had his seizure attack (1st episode) which lasted for 20 min according to his caretaker which was his wife. During this period, the caretaker called the emergency care line for ambulance assistance. Caretaker

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claims, no up-roll eyeballs, no incontinence, no drooling of saliva and the attack aborted naturally. After approximately 10 min it aborted, at 2330H he experienced 2nd episode with similar gesture which lasted for approximately 2 min. This period, a Medical Assistant (MA) had arrived and aborted with intravenous (IV) diazepam 2.5mg stat at his home. He was then monitored and decided to be transported to TMAFH. On 17th August 2018 at 0110H, in the ambulance patient experienced 3rd episode. This was aborted with IV diazepam 2.5mg stat again. At Emergency Department (ED), his case was treated as breakthrough seizure. On 17th August 2018 at 0400H, patient was IV infusion of phenytoin 800mg in 100mL normal saline over 1 hr. Computed Tomography (CT) brain results show right cerebral atrophy with focal cortical density at frontal lobe. Upon retrieving and reviewing his past medical records, this was his fifth admission of the year to the hospital for breakthrough seizure. The medical team was asked to review him and decided to admit him and monitor to rule out sub therapeutic level of AED.

During day 1 at ward, previous medication of tablet VPA 400mg TDS was continued with addition of tablet phenytoin 300mg OD. Tablet VPA was served at 0600H, 1400H and 2200H while tablet phenytoin was served at 2200H. TDM level was taken for both drugs. Day 2 at 1600H, pharmacist reviewed TDM results and advised for tablet VPA evening dose to withhold as level was toxic. Tablet levetiracetam 500mg BD was suggested instead of tablet phenytoin. This suggestion was accepted by prescribers. Day 3 at ward upon reviewing VPA TDM results, patient was discharged with tablet VPA 400mg BD; daily dose of 800mg (20mg/kg/day) and tablet levetiracetam 500mg BD.

DISCUSSION

In pharmacokinetics view, VPA is absorbed almost complete and rapid in fasting patients after oral intake. The peak blood levels occur within 1 to 4 hr.[2] Overall absorption is delayed but extent is not affected if the medicine is taken with food. Due to transformation of sodium valproate into valproic acid, gastric irritation occurs with plain tablet, sugar-free liquid or when administered during empty stomach. This will not occur with enteric-coated tablets. Daily drug dose of 1,200 to 1,500 mg will cause therapeutic plasma levels of 50-100 microgram/mL (0.35-0.69 mmol/L). There is a poor correlation between daily dose per bodyweight and plasma levels. Hence, TDM comes into requirement. VPA is rapidly distributed and is restricted due to the circulation and rapidly exchangeable extracellular water. Due to concentration-dependent plasma protein binding and relatively short half-life, VPA is non-linear kinetics.

VPA is bounded by approximately 90% to plasma proteins but only 60% to albumin. If plasma level rises above 120 microgram/mL or if the serum albumin concentration is lowered, the binding sites may become saturated. This causing the amount of free drug to rise rapidly, out of proportion to any increase in dosage. Phenobarbitone and phenytoin maybe displaced from plasma protein binding sites by VPA.[3] VPA crosses the placenta in animal model. VPA metabolism is complex. The major elimination pathway is via glucuronidation (40-60%) and remainder is metabolized using oxidation; β-oxidation accounting for 30-40% and w-oxidation (cytochrome P450 dependent). Only 1 to 3% of the ingested dose is found to be excreted unchanged in the urine. VPA is almost completely metabolized prior to excretion. Plasma half-life is variable but generally appears to be 8 to 12 hr (range 3.84 to 15.77 hr). It can be less if patients receive other AEDs if patients have been on the drug for a long duration. In cases of overdose, long half-lives up to 30 hr have been reported. Antipsychotic agents or antidepressants co-administered will result in competitive metabolism or enzyme inhibition, thereby increasing VPA levels.[4] This is the main cause of interactions with other class of medicines. If the initial AED is VPA then phenytoin is added, there will be a decrease in serum concentration of VPA as metabolism is increased.[5]

CONCLUSION

This was a clear case study where the initial AED which was VPA was not monitored intensively to achieve desired clinical outcome. The clinical team did not apply the pharmacology aspect of VPA (enzyme inhibitor) to achieve seizure control. Phenytoin (enzyme inducer) was added to therapy and then de prescribed. VPA maintenance dose was sub therapeutic for the patient. Clinical pharmacology should be applied in patient care management. Patients also needs to be informed about the disease, prognostic implications, Objectives of therapy, risks and benefits of treatment. This includes the risks associated with poor compliance. With an improved integrated care involving sequential TDM, the clinical focus on achieving 12-month remission therapeutic aim is achievable.

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CONFLICT OF INTEREST

The authors declared that they have no conflicts of interest

ABBREVIATIONS

Nil.

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