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CASE REPORT

Potential Valproate Acid Interaction with Enteral Feedings - A Case Report.

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Abstract

For most antiepilepsy drugs including valproic acid (VPA), co-administration with food can slow down the absorption rate, but this does not have a clinically relevant effect on the extent of absorption and area under the curve. However, limited data are available on enteral nutrition interaction with VPA. Nonetheless, it is possible for a medication to have a lack data on drug-food interactions but have significant absorption changes when co-administered with enteral nutrition. We describe a case of a 32-year-old man with myoclonic jerking movement at both upper limbs and lower limbs with underlying diffuse cortical dysfunction. The patient receiving enteral VPA syrup dose experienced a clinically significant decrease in serum concentration when high protein enteral feeding was initiated. There was no significant change in VPA serum concentration although the doses were separated from the feeding by two to three hours. By escalating the dosing frequency of VPA from BD to TDS, it significantly increased VPA serum concentration. The interaction between nutrients and highly protein-bound drugs is a problem of great relevance in clinical practice due to potential changes in the expected effects of the drug. The clinical practice of separating phenytoin from enteral feeding was applied in this case however, it was unsuccessful. Therefore, when using enteral feeding concomitantly with enteral VPA, clinicians may consider increasing VPA frequency to TDS dosing.

Keywords: valproic acid, enteral feeding, serum concentration

Introduction

Valproic acid (VPA) is one of the most widely prescribed antiepileptic drugs (AEDs) for the treatment of epileptic seizures. It has been proposed that VPA potentiates gamma aminobutyric acid (GABA) effects in the central nervous system.[1] Impairment of GABAergic inhibitory activity can lead to convulsions, making the control of this pathway a target for AEDs.[2]

VPA is a narrow therapeutic index drug with high pharmacokinetic variability. It is highly protein bound (87 to 95%) and has low clearance (6 to 20 ml/h/kg).[2] VPA is available in several formulations including intravenous (IV) solution, capsule, tablet, enteric-coated tablet, sustained-release tablet and oral solution. However, the rate of VPA absorption and bioavailability are different among formulations. The bioavailability of VPA is documented as approaching one for IV solution, oral solution and capsules, while approximately 0.8 to 0.9 for sustained-release tablets. The durations to achieved maximum concentration of VPA are one to two hours, three to six hours and 10 to 12 hours for oral solution, enteric-coated tablet and sustained-release tablet formulations, respectively.[1]

Protein-binding is linear for most AEDs and the percentage of free fraction is a constant within serum concentration. VPA is however, the single exception. Its free fraction is concentration-dependent as protein-binding is decreased markedly at high serum concentration due to protein-binding site saturation.[3]

For most AEDs including VPA, co-administration with food can slow down the absorption rate, but this does not have a clinically relevant effect on the extent of absorption and area under the curve. Consequently, most AEDs can be administered with or without food.[3] However, limited data are available on enteral nutrition interaction with VPA. Nonetheless, it is possible for a medication to lack data of drug-food interactions but have significant absorption changes when co-administered with enteral nutrition. This is because the enteral nutrition can slow down the gastric emptying and thus, decreasing the bioavailability of drugs which lead to impaired drug absorption.[4]

Case Report

A 32-year-old man was admitted to intensive care unit (ICU) due to acute exacerbation of asthma secondary to community acquired pneumonia. He was sedated and intubated with intravenous infusion (IVI) of fentanyl 50mcg/hr, IVI midazolam 7ml/hr and IVI propofol 120mg/hr. He was also prescribed with IV piperacillin 4g + tazobactam 500mg for his infection. He was put on nasogastric tube feeding during the ICU stay. The patient however, was having persistent myoclonic jerking movements at both upper limbs and lower limbs. Electroencephalography (EEG) did show abnormal EEG consistent with moderate diffuse cortical dysfunction. He was loaded with IV phenytoin 15mg/kg in 500mL normal saline and was also started with maintenance dose of syrup VPA 400 mg BD, as well as tablet clonazepam 2 mg TDS. The jerking movements were still frequent with 8 to 15 episodes lasting for 5 to 20 seconds. Jerking movements of more than two minutes were aborted with suppository diazepam. Tablet levetiracetam 1g BD was then started since the patient's fitting status was still not controlled. Therapeutic drug monitoring (TDM) of VPA three days after dose initiated showed subtherapeutic level of 7.91mg/L. The target range for VPA in seizure is between 50 to 100 mg/L. The subsequent dose of 600mg BD was then given two to three hours apart of the feeding and the concentration of VPA increased to 12.9mg/L only. Jerking episodes were still not reduced as the level was still subtherapeutic. VPA dose was later increased to 600mg TDS and was continued to be given at two to three hours apart of the feeding. TDM was again utilized and the concentration increased to 54.08mg/L. In line with VPA level, fitting episodes were reduced to three to four times a day, lasting for five to 10

seconds. VPA was increased once more to 700mg TDS and jerking movement was no longer seen for two days after the dose optimization. The patient was discharged after 24 days of treatment.

Discussion

VPA is the first generation AEDs for the treatment of seizure. The initial dose of VPA is usually 400 to 600mg/day in adult followed by maintenance dose of 400 to 2500mg/day and commonly given as twice daily dosing.[5] Because VPA has a narrow therapeutic index, TDM of VPA is a crucial part of the drug therapy. The recommended VPA therapeutic range for the treatment of epilepsy is 50 to 100mg/L. A slightly higher range of 50 to 125mg/L is proposed for bipolar disorder therapy.[1] This report described a case of an enteral feeding resulting in altered absorption of VPA. Although there is a lack of literature to support significant VPA-food interactions, it does not rule out the possibility of VPA interaction with enteral feeding.

Enteral nutrition administration via a feeding tube is the preferred method of nutritional support in a patient with functional gastrointestinal tract but is unable to be fed orally and this procedure is commonly used in ICUs to keep an adequate supply of nutrients. Administering oral medications to patients with nasogastric tube feeding is a challenging patient-care issue. The interaction between nutrients and drugs is a problem of great relevance in clinical practice due to potential changes in the expected effects of the drug. The possible interactions may impair the action of the drug and/ or food, which may cause an inappropriate pharmacological effect of the drug or a compromised nutritional status, in addition to the obstruction of feeding tubes. All of these factors may result in a greater cost and length of hospital stay. [6]

When taken orally, a medication is dispersed and dissolved in the stomach, followed by dissolution and absorption in the intestine. Passing through the stomach via a feeding tube will impacts the dissolution and absorption of certain drugs. A drug that is a weak acid such as VPA, will be absorbed primarily in the acidic environment. If not given in stomach, the bioavailability of VPA may be reduced, and therefore leads to a reduction in the concentration of the drug.[4]

The clinical practice of separating phenytoin from enteral feeding was applied in this case since the VPA level was too low, nonetheless, it was unsuccessful. With the escalation of the dosage and administrations of VPA separated by two to three hours apart from the enteral feedings, the level only managed to increase by 5 mg/L. The practice however, was successful in a previous case reported by VandenBerg and Broadway, 2018.[7] Clinical Practice Guideline by University of Wisconsin Hospitals and Clinics Authority on Dosing of Medications in Patients Receiving Continuous Enteral Feedings suggested administering VPA solution dosed every six to eight hours with close monitoring of VPA levels.[8] With an increased frequency of VPA to TDS dosing, our patient showed a significant clinical improvement with increased in VPA level within the target range.

Conclusion

We present a case report of a possible interaction between VPA and enteral feeding. Low VPA serum levels were observed during concomitant administration with enteral feeding. It is important for the clinicians to recognize potential interaction and impaired absorption of VPA with enteral feeding. To avoid unsuccessful seizure abortion, clinicians may consider increasing VPA frequency to TDS dosing.

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Author Contributions

SM drafted the article, revised it critically and gave final approval of the version to be published. SLA was involved in the drafting of the article, literature review and critical revision and gave final approval of the version to be published. SHM and NLA drafted the article and revised it critically.

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