PSYCHIATRIC MANAGEMENT OF THE MEDICALLY COMPLICATED PATIENT

mhc MENTAL HEALTH CLINICIAN

CASE REPORT Open Access

Enteral administration of protein supplement and valproate: A potential pharmacokinetic interaction

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How to cite: VandenBerg A, Broadway J. Enteral administration of protein supplement and valproate: A potential pharmacokinetic interaction. Ment Health Clin [Internet]. 2017;7(1):10-2. DOI: 10.9740/mhc.2017.01.010.

Abstract

Background: Valproic acid (VPA) and its derivatives are highly protein bound. Certain highly protein bound medications (eg, phenytoin) have specific administration instructions for patients on enteral nutrition supplements to optimize absorption of the medication. Pharmacokinetic interactions between VPA and enteral nutrition or protein supplements demonstrating impaired absorption have not been published to date.

Case Report: A patient receiving enteral VPA syrup via percutaneous endoscopic gastrostomy tube experienced a clinically significant decrease in serum concentration when enteral protein supplement was initiated. Other sources of interactions were ruled out, and VPA serum concentration increased when doses were separated from protein supplement by 2 hours.

Discussion: This is the first published case of enteral protein supplementation affecting absorption of enteral VPA. Enteral feeds are known to interact with other highly protein bound medications, and clinical practice for these medications may be used to guide administration when an interaction with VPA is suspected.

Conclusion: When using enteral protein supplements concomitantly with enteral VPA, clinicians may consider separating doses to avoid potential interaction or impaired absorption.

Keywords: valproate, valproic acid, protein binding, enteral nutrition, serum concentration

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Disclosures: The authors have no conflicts of interest to disclose. No financial support was received for this article

Introduction

Valproic acid (VPA) and its derivatives are available in many dosage forms, including parenteral injection, oral liquid, immediate-release gel capsules, delayed-release tablets/capsules, and extended-release tablets. The dosage forms are marketed under multiple brand names and are variably indicated for the treatment of epilepsy and manic episodes of bipolar disorder and for the prevention of migraine headaches.[1,2] The only product available for enteral administration is VPA syrup.

The pharmacokinetics of VPA products are characterized by almost complete absorption.[2] Different formulations may result in different time to maximum serum concentration or maximum serum concentration, but the extent of absorption remains relatively unchanged. Valproic acid demonstrates significant protein binding, primarily with albumin, resulting in a dose-dependent free fraction of 5% to 15% with low doses and up to 30% with higher doses.[2]

Hepatic metabolism accounts for nearly all VPA metabolism via glucuronidation (30% to 50%), mitochondrial beta-oxidation (>40%), and other oxidative pathways (15% to 20%).[1] A number of medications interact with

VPA via alteration of cytochrome P450 enzymes (2C9 and 2C19).[1,2] Carbamazepine, phenytoin, phenobarbital, primidone, and isoniazid are known inducers of VPA metabolism, which can result in significantly lower serum concentrations. Doses 2-fold to 3-fold higher may be required to achieve desired serum concentration when VPA is used concurrently with these inducers. Additionally, aspirin has been reported to significantly increase free fraction of VPA via displacement from albumin binding sites.[3] Hypoalbuminemia has also been associated with increased free fraction of VPA due to decreased protein binding.[4]

Food does not appear to have a clinically significant impact on VPA pharmacokinetics. When taken with food, delayed absorption may result in a longer time to maximum serum concentration and lower maximum serum concentration; however, total absorption and area under the curve are relatively unchanged.[5-10] Data are lacking regarding whether enteral nutrition interacts with VPA.[5-10] It is possible for a medication to lack drug-food interactions but have significant absorption changes when enterally coadministered with enteral nutrition.

Food does not affect absorption of oral phenytoin; however, the highly protein bound antiepileptic medication is known to interact with enteral nutrition, thereby resulting in a decrease of up to 90% in absorption of medication.[11-13] The apparent mechanism of this interaction is via binding to proteins in enteral supplements, which may vary in significance depending on type of protein and binding to the feeding tubes.[13] Standard practice is to separate enteral feeds and administration of phenytoin suspension by at least 2 hours based on these data (holding feeds for 1 hour before and 1 hour after phenytoin dose).

Since proteins are a potential source of interaction between medications and enteral nutrition, protein supplements should also be considered. Pro-Stat® is a liquid protein supplement used for a variety of indications including pressure ulcers, malnutrition, and hypoalbuminemia.[14] The supplement contains hydrolyzed collagen protein. Pharmacokinetic studies evaluating how this protein affects VPA absorption are not available.

Case: Impact of Enteral Protein Supplement on Enteral VPA Absorption

A 57-year-old man with a history of severe cerebral palsy, associated mood and behavioral issues, and severe paranoia at times was followed in a nursing home for many years and had been on multiple medications to help improve his behavior. He had been doing well on a combination of VPA and a low dose of clonazepam and aripiprazole for almost a year; however, his behavior worsened in the context of aripiprazole discontinuation during a hospitalization for urosepsis. At follow-up, negative behaviors persisted despite restarting and titrating aripiprazole. At that time (day 1), a random serum VPA concentration drawn 7 hours after dosing was 40.7 µg/mL, corresponding to a dose of 1000 mg twice daily (weight 100 kg). On day 8, enteral protein supplement was added for protein malnutrition (albumin 3.3 g/dL). On day 18, VPA was increased to 1250 mg twice daily to target persistent behavioral issues. When checked on day 28, the 7-hour serum concentration decreased to 13.9 µg/mL. Again the dose was titrated, now to 1500 mg twice daily, and the 8-hour serum concentration came back unchanged on day 42 (13.9 µg/mL). Neither noncompliance nor "cheeking" were a concern as he was getting his medications via a percutaneous endoscopic gastrostomy (PEG) tube. A thorough review of his medications revealed only the protein supplement as a theoretical source of interaction. These supplements were being given via PEG twice daily with VPA liquid. While the specific administration sequence was not specified in the record, it was standard practice at the facility for medications to be given sequentially, each followed by flushing the PEG tube with water. The only other medication changes during this period were a 10-day course of cephalexin, a change in brand of iron supplement, and a 5-day course of magic mouthwash oral swabs. Given the temporal relationship between initiating protein supplement and VPA serum concentration decrease and the lack of another explanation for the change, the administration of the 2 products was separated by 2 hours. Subsequently, on day 59, the VPA concentration increased from 13.9 µg/mL to 56.5 µg/mL with no change in dose (serum albumin 3.1 g/dL). At the next follow-up visit, his behavior was reportedly "much improved," per staff at the nursing facility.

Discussion

This is the first published case of an enteral protein supplement resulting in altered absorption of VPA. While VPA does not demonstrate significant drug-food interactions, that does not rule out the possibility of interaction with enteral supplements. Phenytoin is a commonly known example of this phenomenon. Since there is a dearth of literature regarding this type of interaction with VPA, the clinical practice of separating medication doses from enteral supplements was used to guide practice in this case with clinical success. While phenytoin may also bind to tubing, there is no literature to suggest that this type of binding would or would not occur with VPA. In this case, it is unlikely that the VPA was bound to tubing, as the patient had been receiving VPA via PEG prior to the protein supplement. This report is limited by being a single

case without rechallenge. While other potential causes were considered ruled out, rechallenge with concurrent dosing would help support the interaction. Given the decompensation the patient had previously experienced, it was not ethical to resume concurrent administration for the purpose of assessing pharmacokinetic parameters.

Conclusion

To avoid potential interaction and impaired absorption, clinicians may consider separating enteral VPA doses from enteral protein supplements or enteral feeds by 2 hours. Whether this only applies to PEG or nasogastric tube administration of liquid VPA and hydrolyzed collagen protein or applies to all oral formulations of VPA and all protein/nutrition supplements is yet to be seen.

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