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POTENTIAL PHARMACOKINETIC INTERACTION BETWEEN ENTERAL NUTRITION AND VALPROIC ACID

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ABSTRACT

Background: Certain scientific publications suggest that medications with high protein binding, such as phenytoin, have lower-than-expected serum levels in patients receiving enteral nutrition (EN) preparations or nutritional supplements. Valproic acid (VPA) is highly protein bound but currently no interactions with EN that would reduce serum levels have been documented.

Case description: A 69-year-old patient receiving enteral VPA oral solution via a nasojejunal tube experienced a clinically significant decrease in serum concentration when EN was initiated. Other sources of interactions were ruled out, and VPA serum concentration increased when doses were separated from EN by one hour.

Discussion: Interactions between highly protein bound compounds and EN have been previously described for other medications. However, there is a lack of data regarding the interaction between EN and VPA; only one published case has involved a protein supplement administered via percutaneous endoscopic gastrostomy. In our case, adjusting the timing of medication administration relative to enteral feeding resulted in increased serum VPA levels, which correlated with an improvement in clinical outcomes, suggesting the potential interaction.

Conclusion: These findings suggest a potential interaction between EN and the absorption of VPA, which may lead to reduced drug absorption and significant clinical implications.

KEYWORDS

Valproic acid, enteral nutrition, drug interaction, therapeutic drug monitoring

LEARNING POINTS

- Enteral nutrition may reduce the absorption of valproic acid. This could potentially result in subtherapeutic serum levels and worsen clinical outcomes.
- Clinicians should closely monitor serum levels and consider separating the administration of valproic acid and enteral nutrition by at least one hour.

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INTRODUCTION/BACKGROUND

Valproic acid (VPA) is a widely used medication for treating various types of epilepsy, bipolar disorder and certain neurological conditions such as migraines and neuropathic pain[1,2]. Despite extensive research, its precise mechanism of action remains incompletely understood. However, substantial evidence suggests that VPA increases the synthesis of gamma-aminobutyric acid (GABA) and decreases glutamate synthesis through the activation of N-methyl-D-aspartate (NMDA) glutamate receptors. Moreover, VPA also exerts its effects by blocking voltage-dependent sodium channels[3].

The pharmacokinetics of VPA are characterised by nearly complete oral bioavailability. Approximately 90% of VPA binds to plasma proteins, mainly albumin; this binding is dose-dependent and saturable, a factor that – along with its narrow therapeutic range and high pharmacokinetic variability – justifies the monitoring of its plasma levels[3]. VPA is available in different dosage forms including parenteral injection, oral solution, gastro-resistant tablets and extended-release tablets.

Certain scientific publications suggest that medications with high protein binding, such as phenytoin, may have lower-than-expected serum levels in patients receiving enteral nutrition (EN) and/or nutritional supplements[4]. Currently, there is no documented interaction between VPA and EN that would reduce serum levels. Food does not appear to have a clinically significant impact on VPA pharmacokinetics, but this does not exclude the possibility of such interactions with enteral feeding[5].

CASE DESCRIPTION

A 69-year-old woman with a history of bipolar type 1 disorder, under treatment with extended-release-valproic acid 500 mg every 12 hours, extended-release quetiapine, immediate-release quetiapine and aripiprazole, was admitted to the San Carlos Clinical Hospital for acute gangrenous cholecystitis associated with duodenal perforation. An urgent laparoscopic cholecystectomy and duodenal repair were performed.

The patient remained in the General Surgery ward and was placed on a nothing-by-mouth (NPO) regimen, with the exception of her usual oral medication, which was initially administered in tablet form (500 mg of VPA every 12 hours orally). On day six of admission, the Psychiatry department, in collaboration with the General Surgery team, considered it more appropriate to switch the formulation to an oral solution of VPA at the same dose (500 mg every 12 hours) to facilitate administration. On day eight, serum VPA control levels were 32.7 µg/ml, drawn 11 hours after the last dose.

Initially, nutrition was maintained by parenteral administration, later transitioning to EN on day 13. A nasojejunal tube was inserted for feeding, and EN was initiated via a 24-hour continuous infusion pump. While maintaining the same VPA dose (500 mg every 12 hours) and formulation, new serum levels were requested on day 18, but the results were undetectable. However, given the patient's clinical stability, the VPA treatment was discontinued.

Subsequently, the patient experienced a deterioration in her psychiatric condition, prompting the reintroduction of VPA treatment. On day 25, the Clinical Pharmacology department recommended resuming VPA as an oral solution (500 mg daily) at 10 PM, administered one hour apart from EN, which was provided from 9 AM to 9 PM. On day 28, VPA serum levels, measured 11 hours after the last dose, increased to 16.5 µg/ml. To achieve therapeutic levels, the VPA dose was increased to 1,000 mg at 10 PM, maintaining the 1-hour separation from EN. By day 32, the serum concentration had risen to 37.5 µg/ml. The patient's clinical progress, both in terms of her psychiatric condition and postoperative recovery, was favourable and without complications.

Therapeutic adherence was ensured as the medication was administered via a nasojejunal tube under the supervision of nursing staff. A thorough review of her medications revealed that EN was the only potential source of interaction. No other medication changes were identified that could have caused an interaction. Due to the temporal relationship between the start of enteral feeding and the decrease in serum VPA concentration, and in the absence of any other explanation for the changes in concentrations, the administration of the two products was separated by at least one hour, which resulted in an increase in VPA concentration.

DISCUSSION

To our knowledge, this case represents the first documented instance of potentially impaired absorption of VPA likely due to concomitant administration with EN. Although no interactions with food have been reported, this does not exclude the possibility of such interactions with enteral feeding. There is a lack of data regarding whether EN interacts with VPA, and only one published case involving an enteral protein supplement administered via percutaneous endoscopic gastrostomy has suggested altered absorption of VPA[6].

However, phenytoin is a well-known example of this phenomenon. The concurrent administration of phenytoin and EN can reduce phenytoin absorption by up to 70%, resulting in subtherapeutic serum drug levels. This interaction was first reported by Bauer in 1982 in neurosurgical patients receiving continuous nasogastric tube feedings and phenytoin suspension. The author recommended discontinuing enteral feeding two hours before and two hours after phenytoin administration and flushing the feeding tube with 60 ml of water post-administration[4].

The precise mechanism underlying this interaction has yet to be elucidated. However, it is believed to be related to the binding of phenytoin to the protein or calcium content of EN, or to phenytoin directly binding to the material of the gastric tube itself[7,8]. Despite the mechanistic uncertainty, many institutions have implemented practices to mitigate the phenytoin-feeding interaction. These include dose increases

to account for lower bioavailability, routinely holding EN for administration, continuation of IV dosing until the patient no longer requires continuous EN or using alternative dosage forms such as administering IV fosphenytoin via the feeding tube[9,10].

Despite the lack of literature confirming whether a similar interaction occurs with VPA, in this case serum VPA levels increased after the timing of medication administration was adjusted relative to enteral feeding, correlating with an improvement in clinical outcomes. It is unlikely that VPA bound to the enteral feeding tube, as the drug was consistently administered via an oral solution through the tube, even when serum levels rose.

However, this report is limited by being a single case. Further pharmacokinetic studies in patients are needed to clarify this interaction and possible cofounding factors. It is essential to determine whether it is specific to the oral solution of VPA used in conjunction with EN, or if it also extends to all oral formulations of VPA and various protein supplements.

CONCLUSIONS

These findings suggest a potential interaction between enteral feeding and the absorption of valproic acid, akin to the interaction observed with phenytoin. This interaction may lead to reduced drug absorption and significant clinical implications. To minimise this risk, it is advisable for clinicians to separate the administration of valproic acid from enteral feeding by at least one hour. Nevertheless, further studies are required to clarify this interaction and possible cofounding factors.

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