

# Meropenem-induced Valproic Acid Elimination: A Case Report of Clinically Relevant Drug Interaction

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**Abstract:** We present two case reports of drug interaction between valproic acid and meropenem. In comparison with expected population-kinetic based serum levels, we observed 90.8 and 93.5% decrease in valproic acid serum levels during concomitant administration with meropenem. If carbapenems need to be administered to valproic acid treated patient, other anticonvulsant addition seems to be the appropriate as most probably the valproic acid dose escalation would not be sufficient to achieve therapeutic serum concentration.

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## Introduction

Valproic acid (2-propylpentanoic acid, VPA) was introduced for clinical use in France in 1967. Over the next half-century it has become a well-established first-line and widely used agent for convulsion treatment both for its broad spectrum of activity against generalized and partial seizures and for its acceptable safety profile (Peterson and Naunton, 2005). VPA serum therapeutic range is 50–100 mg/l (346–693  $\mu\text{mol/l}$ ) in seizure treatment (Bentué-Ferrer et al., 2010). Although VPA therapeutic drug monitoring is not routinely recommended in common neurological practice (Tomson et al., 2007) it can be useful in polypharmacy to reveal possible drug interactions or in the intensive care units when VPA is initiated for the onset of seizure treatment (Loh et al., 2010).

There are at least three metabolic pathways of VPA elimination in humans: glucuronidation, mitochondrial beta-oxidation (both considered major routes accounting for 50 and 40% of dose, respectively) and cytochrome P450-mediated oxidation (minor route responsible for elimination of approximately 10% of dose) (Ghodke-Puranik et al., 2013). Concurrently, VPA is regenerated from VPA-glucuronide by acylpeptide hydrolase-mediated hydrolysis. Carbapenems inhibit acylpeptide hydrolase and thus VPA regeneration from VPA-glucuronide, resulting in reduced VPA serum levels (Nakajima et al., 2004; Suzuki et al., 2010, 2011).

There are few case reports describing decreased VPA serum levels by carbapenems (Nacarkucuk et al., 2004; Clause et al., 2005; Fudio et al., 2006; Suntimaleeworakul et al., 2012). A recent study also documented the decreased VPA levels caused by concomitant use of meropenem using a large number of therapeutic drug monitoring (TDM) records (Wen et al., 2017). We present additional two cases of this significant drug interaction.

## Case report 1

A 59-year-old polymorbid male (90 kg, 180 cm) admitted to the Department of Anesthesiology and Intensive Care after cardiopulmonary resuscitation for cardiorespiratory arrest. The sixth day of hospital stay VPA treatment was initiated for generalized myoclonic seizures probably related to brain ischemia. Patient was loaded with 1,600 mg VPA administered via 24 h-continuous intravenous infusion, followed by maintenance doses of 500 mg given every 8 hours as crushed slow-release tablets through the nasogastric tube. The tenth day of hospital stay meropenem therapy was initiated (2 g intravenous bolus followed by 4 g/day in continuous intravenous infusion) for pulmonary infection. The other concomitant medication included norepinephrine, unfractionated heparin (UFH), insulin, propofol, potassium supplementation, omeprazole, prednisone, diosmectite and probiotics. After five days of concomitant VPA and meropenem administration, blood sample was taken, showing a serum level of VPA of 8.0 mg/l (determined using a cloned enzyme donor immunoassay with quantification limit of 3 mg/l). In

spite of the low VPA levels no other seizures episode occurred. Subsequently VPA treatment was discontinued.

### Case report 2

A 56-year-old man (92 kg, 178 cm) with chronic thrombotic pulmonary hypertension was admitted to the surgical ward for elective pulmonary vein endarterectomy. Patients' medical history included congestive hepatopathy, history of minor stroke, mild chronic kidney disease, dyslipidemia, hypertension and schizophrenia. On the second postoperative day after successful surgery intravenous meropenem 2 g three times a day was initiated because of pulmonary infection. As generalized myoclonic seizures occurred the day after, VPA treatment was initiated. Intravenous loading dose of 1,200 mg was followed by 100 mg/hour continuous infusion for 24 hours. Subsequently the patient was treated with maintenance doses of 300 mg every 8 hours administered as crushed slow release tablets through the nasogastric tube. On the postoperative day 7 the trough level of VPA was 3.4 mg/l (determined using cloned enzyme donor immunoassay). Concomitant medication included norepinephrine, UFH, insulin, propofol, sufentanyl, potassium supplementation, vancomycin, acetaminophen, dipyron, omeprazole, furosemide, risperidone and treprostinil. In spite of the low VPA levels no other seizures episode occurred through the rest of hospital stay. Meropenem was withdrawn on postoperative day 8 and VPA two weeks later shortly before the hospital discharge.

### Discussion

Food and Drug Administration Professional Drug Information (FDA-PDI) states following mean VPA population pharmacokinetic parameters: volume of

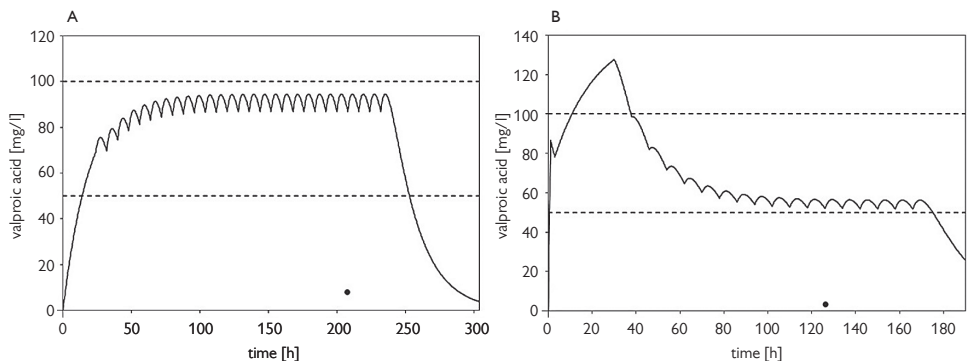


Figure 1 – A priori simulation of valproic acid plasma levels time profile based on population pharmacokinetics compared with measured valproic acid concentration. A) case report 1; B) case report 2. Dotted lines represent therapeutic range.

distribution 11 l/1.73 m<sup>2</sup>, clearance 0.56 l/h/1.73 m<sup>2</sup> and terminal elimination half-life ( $T_{1/2}$ ) 16 h. Simulation of VPA serum levels based on FDA-PDI population pharmacokinetics compared with measured VPA concentration is shown in Figure 1. Pharmacokinetic models show that measured VPA serum concentrations corresponded to only 9.2 and 6.5% of concentrations estimated based on population data. Fitting of the simulated pharmacokinetic profile curve with observed drug concentration points resulted in VPA  $T_{1/2}$  of 1.6 and 1.4 h. Very short  $T_{1/2}$  indicates that VPA dose escalation is meaningless in this case, while switch to another antiepileptic agent seems to be more relevant for effective anticonvulsive treatment.

It should be noted, however, that in theory the case 1 VPA levels could be also affected by reduced VPA absorption due to concomitant diosmectite administration. However, diosmectite was administered in at least 2 h distance from the other medication and no adsorbent was administered to the patient in case 2 where comparably low concentration of VPA was measured. In both cases slow release tablets were crushed to allow administration through nasogastric tube. Nevertheless nasogastric tube should have negligible impact. VPA bioavailability is approaching 100% when immediate release form is used and 8 hour dosing interval would not result in as low serum trough levels as were measured if clearance of the drug was not affected. Based on the literature data VPA-meropenem interaction is the most probable explanation for this observation. As absorption extent and volume of distribution is likely not to be affected by concomitant meropenem administration, significant increase in VPA clearance due to inhibition of VPA-glucuronide cleavage is most probable mechanism of this interaction.

Carbapenems are known for seizure threshold lowering properties in comparison with non-carbapenem antibiotics. Even though this adverse event was described mostly for imipenem/cilastatin, head to head comparison with meropenem showed similar risks for imipenem and meropenem (Cannon et al., 2014). In case 2, possible contribution of meropenem in triggering seizures cannot be excluded. Considering carbapenem-VPA interaction, appropriate treatment of suspected carbapenem-induced seizures should not include VPA.

## Conclusion

We present two case reports of drug interaction between VPA and meropenem. In comparison with expected population-kinetic based serum levels, we observed 90.8 and 93.5% decrease in VPA serum levels during concomitant administration with meropenem. It is important for the physicians to recognize drug interaction between VPA and carbapenems, especially when treating carbapenem induced seizures. If carbapenems need to be administered to VPA treated patient other anticonvulsant addition seems to be appropriate as VPA dose escalation would most probably not be sufficient to achieve therapeutic serum concentration.

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