The carbapenem antimicrobial meropenem has a broad spectrum of activity against most Gram-positive and Gram-negative bacteria, including organisms producing beta-lactamase. It is licensed for several indications in the US and the UK, including pneumonia, skin infections and intra-abdominal infections. Its use to treat urinary tract infections is licensed in the UK but not in the US.

Valproic acid (VPA) undergoes hepatic metabolism rapidly and extensively. It is metabolised by the cytochrome P450 enzyme system so is susceptible to many drug-drug interactions. Manufacturers report that VPA plasma levels decrease significantly (with a corresponding reduction in anticonvulsant effect) when the drug is administered concomitantly with carbapenems, although the exact mechanism of this interaction is unknown (see Box, p182). Such interactions have occurred with meropenem, imipenem, ertapenem and doripenem. The results of some human and animal studies suggest that meropenem is less neurotoxic than imipenem/cilastatin. Consequently, meropenem has been used in place of imipenem/cilastatin for patients who have a history of seizure disorders.

This report describes a case where an interaction between VPA and meropenem led to the patient experiencing several epileptic seizures.

The case

A 55-year-old, 102kg Caucasian male, with a history of seizures and multiple sclerosis, complicated by quadriplegia and dysphagia, was transferred to Veteran Affairs Medical Centre in Long Beach, California, for the treatment of urosepsis, *Clostridium difficile* colitis and aspiration pneumonia (sputum samples had tested positive for *Klebsiella* spp and *Pseudomonas*).
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Significantly after meropenem treatment seizures. Valproate levels only increased loading doses, resulted in recurrence of an increased maintenance dose and multiple seizures, have been reported recently.5,15–17 In our patient, reduced valproate serum concentrations following concomitant administration of carbapenem antibiotics, leading to a decreased level of circulating drug. However, this accumulation is small and its significance not proven.6 Systemically absorbed VPA is glucuronidated by the liver to become VPA-glu, which is excreted by the kidneys. Consequently, researchers have proposed that carbapenems might:

- Enhance the rate of glucuronidation of VPA by the liver1,3,8
- Hasten the renal clearance of VPA-glu
- Inhibit the bacterial beta-glucuronidase enzyme that hydrolyses VPA-glu to VPA (as described above) leading to a decreased serum level of VPA10

Perhaps, one or a combination of these mechanisms are responsible for the carbapenem-mediated reduction in plasma valproate level.

References


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